



For the use only of registered medical practitioners or  
a hospital or a laboratory.

## Ruxolitinib 5 mg, 10 mg, 15 mg and 20 mg tablets

### Jakavi®

Protein kinase inhibitors.

### DESCRIPTION AND COMPOSITION

#### Pharmaceutical forms

5 mg tablets: round curved white to almost white tablets with 'NVR' debossed on one side and 'L5' debossed on the other side

10 mg tablets: round curved white to almost white tablets with 'NVR' debossed on one side and 'L10' debossed on the other side

15 mg tablets: ovaloid curved white to almost white tablets with 'NVR' debossed on one side and 'L15' debossed on the other side

20 mg tablets: elongated curved white to almost white tablets with 'NVR' debossed on one side and 'L20' debossed on the other side

#### Active substance

Ruxolitinib phosphate

Ruxolitinib 5 mg per tablet

Ruxolitinib 10 mg per tablet

Ruxolitinib 15 mg per tablet

Ruxolitinib 20 mg per tablet.

#### Active Moiety

Ruxolitinib.

#### Excipients

Cellulose, microcrystalline

Magnesium stearate

Silica, colloidal anhydrous

Sodium starch glycolate (Type A)

Hydroxypropylcellulose

Povidone

Each 5 mg tablet contains 71.45 mg of lactose monohydrate

Each 10 mg tablet contains 142.90 mg of lactose monohydrate

Each 15 mg tablet contains 214.35 mg of lactose monohydrate

Each 20 mg tablet contains 285.80 mg of lactose monohydrate.

## **INDICATIONS**

### *Myelofibrosis*

Jakavi is indicated for the treatment of patients with myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

### *Polycythemia vera*

Jakavi is indicated for the treatment of patients with polycythemia vera who are resistant to or intolerant of hydroxyurea

## **DOSAGE REGIMEN AND ADMINISTRATION**

### **Monitoring instructions**

**Blood cell counts:** a blood cell count must be performed before initiating therapy with Jakavi.

Complete blood counts should be monitored every 2 to 4 weeks until doses are stabilized, and then as clinically indicated (see section WARNINGS AND PRECAUTIONS).

### **Starting Dose**

The recommended starting dose of Jakavi in Myelofibrosis is 15 mg given orally twice daily for patients with a platelet count between 100,000 and 200,000/mm<sup>3</sup> and 20 mg twice daily for patients with a platelet count of >200,000/mm<sup>3</sup>.

The recommended starting dose of Jakavi in Polycythemia vera is 10 mg given orally twice daily.

There is limited information to recommend a starting dose for patients with platelet counts between 50,000/mm<sup>3</sup> and 100,000/mm<sup>3</sup>. The maximum recommended starting dose in these patients is 5 mg twice daily and the patients should be titrated cautiously.

### *Dose modifications*

Doses may be titrated based on safety and efficacy. Treatment should be interrupted for platelet counts less than 50,000/mm<sup>3</sup> or absolute neutrophil counts less than 500/mm<sup>3</sup>.

In polycythemia vera, treatment should also be interrupted when hemoglobin is below 8 g/dL.

After recovery of blood counts above these levels, dosing may be restarted at 5 mg twice daily and gradually increased based on careful monitoring of blood cell counts.

Dose reductions should be considered if the platelet counts decrease below 100,000/ mm<sup>3</sup> with the goal of avoiding dose interruptions for thrombocytopenia. In polycythemia vera, dose reduction should also be considered if hemoglobin decreases below 12 g/dL and is recommended if hemoglobin decreases below 10 g/dL.

If efficacy is considered insufficient and blood counts are adequate, doses may be increased by a maximum of 5 mg twice daily, up to the maximum dose of 25 mg twice daily.

The starting dose should not be increased within the first four weeks of treatment and thereafter no more frequently than at 2-week intervals.

### *Administration instruction*

The maximum dose of Jakavi is 25 mg twice daily.

If a dose is missed, the patient should not take an additional dose, but should take the next usual prescribed dose.

Treatment may be continued as long as the benefit: risk remains positive.

### **Dose adjustment with concomitant strong CYP3A4 Inhibitors or fluconazole:**

When Jakavi is administered with strong CYP3A4 inhibitors or dual moderate inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole), the total daily dose of Jakavi should be reduced by approximately 50% either by decreasing the twice daily dose or by decreasing the frequency of dosing to the corresponding once

daily dose when twice daily dosing is not practical. Avoid the concomitant use of Jakavi with fluconazole doses of greater than 200 mg daily (see section INTERACTION).

More frequent monitoring of hematology parameters and clinical signs and symptoms of Jakavi related adverse reactions is recommended upon initiation of a strong CYP3A4 inhibitor or dual moderate inhibitors of CYP2C9 and CYP3A4 enzymes.

## **Special populations**

### **Renal impairment**

In patients with severe renal impairment (creatinine clearance (Clcr) less than 30 mL/min) the recommended starting dose based on platelet count for MF patients should be reduced by approximately 50%. The recommended starting dose for PV patients with severe renal impairment is 5 mg twice daily. Patients diagnosed with severe renal impairment while receiving Jakavi should be carefully monitored and may need to have their doses reduced to avoid adverse drug reactions.

There are limited data to determine the best dosing options for patients with end-stage renal disease (ESRD) on dialysis.

Available data in this population suggest that, MF patients on dialysis, should be started on an initial single dose of 15 mg or 20 mg based on platelet counts with subsequent single doses only after each dialysis session, and with careful monitoring of safety and efficacy.

The recommended starting dose for PV patients with ESRD on hemodialysis is a single dose of 10 mg, to be administered post-dialysis and only on the day of hemodialysis and with careful monitoring of safety and efficacy (see section CLINICAL PHARMACOLOGY).

### **Hepatic Impairment**

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50%. Patients diagnosed with hepatic impairment while receiving Jakavi should be carefully monitored and may need to have their dose reduced to avoid adverse drug reactions.

### **Pediatrics**

Safety and efficacy of Jakavi in pediatric patients have not been established.

### **Geriatrics**

No additional dose adjustments are recommended for elderly patients.

### **Method of administration**

Jakavi is dosed orally and can be administered with or without food.

## **CONTRAINDICATIONS**

Hypersensitivity to the active substance or any of the excipients.

## **WARNINGS AND PRECAUTIONS**

### **Decrease in blood cell count**

Treatment with Jakavi can cause hematological adverse reactions, including thrombocytopenia, anemia and neutropenia. A complete blood count must be performed before initiating therapy with Jakavi (for monitoring frequency see section DOSAGE REGIMEN AND ADMINISTRATION).

It has been observed that patients with low platelet counts ( $<200,000/\text{mm}^3$ ) at the start of therapy are more likely to develop thrombocytopenia during treatment.

Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily withholding Jakavi. However, platelet transfusions may be required as clinically indicated (see sections DOSAGE REGIMEN AND ADMINISTRATION, and ADVERSE DRUG REACTIONS).

Patients developing anemia may require blood transfusions. Dose modifications or interruption for patients developing anemia may also be considered.

Neutropenia (Absolute Neutrophil Count (ANC) <500/mm<sup>3</sup>) was generally reversible and was managed by temporarily withholding Jakavi (see sections DOSAGE REGIMEN AND ADMINISTRATION, and ADVERSE DRUG REACTIONS).

Complete blood counts should be monitored as clinically indicated and dose adjusted as required (see sections DOSAGE REGIMEN AND ADMINISTRATION, and ADVERSE DRUG REACTIONS).

### **Infections**

Serious bacterial, mycobacterial, fungal, viral and other opportunistic infections have occurred in patients treated with Jakavi. Patients should be assessed for the risk of developing serious infections. Physicians should carefully observe patients receiving Jakavi for signs and symptoms of infections and initiate appropriate treatment promptly. Jakavi therapy should not be started until active serious infections have resolved.

Tuberculosis has been reported in patients receiving Jakavi for myelofibrosis. Before starting treatment, patients should be evaluated for active and inactive ("latent") tuberculosis, as per local recommendations.

Hepatitis B viral load (HBV-DNA titre) increases, with and without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakavi. The effect of Jakavi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

### **Herpes Zoster**

Physicians should educate patients about early signs and symptoms of herpes zoster, advising that treatment should be sought as early as possible.

### **Progressive Multifocal Leukoencephalopathy**

Progressive Multifocal leukoencephalopathy (PML) has been reported with ruxolitinib treatment. Physicians should be alert for neuropsychiatric symptoms suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded.

### **Non-Melanoma Skin Cancer**

Non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and Merkel cell carcinoma have been reported in patients treated with Jakavi. Most of these patients had histories of extended treatment with hydroxyurea and prior NMSC or pre-malignant skin lesions. A causal relationship to ruxolitinib has not been established. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

### **Lipid Abnormalities/ Elevations**

Treatment with Jakavi has been associated with increases in lipid parameters including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Lipid monitoring and treatment of dyslipidemia according to clinical guidelines is recommended.

### **Special populations**

#### **Renal impairment**

The starting dose of Jakavi should be reduced in patients with severe renal impairment. For patients with end stage renal disease on dialysis the starting dose should be based on platelet counts for MF patients (myelofibrosis), while the recommended starting dose is a single dose of 10 mg for PV patients (polycythemia vera). Subsequent doses for both MF and PV patients should be administered only on hemodialysis days following each dialysis session. Further dose modifications should be based on the safety and efficacy of the

drug (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Special populations).

### **Hepatic impairment**

The starting dose of Jakavi should be reduced in patients with hepatic impairment. Further dose modifications should be based on the safety and efficacy of the drug (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL PHARMACOLOGY, Special populations).

### **Interactions**

If Jakavi is to be co-administered with strong CYP3A4 inhibitors or dual moderate inhibitors of CYP2C9 and CYP3A4 enzymes (e.g. fluconazole), the dose should be reduced by approximately 50% (for monitoring frequency see sections DOSAGE REGIMEN AND ADMINISTRATION and INTERACTIONS).

### **Withdrawal effects**

After discontinuation of treatment, myelofibrosis related symptoms are expected to return.

## **ADVERSE DRUG REACTIONS**

### **Summary of the safety profile**

Safety assessment was based on a total of 982 patients (with myelofibrosis or polycythemia vera) receiving Jakavi in Phase 2 and 3 studies.

#### *Myelofibrosis:*

In the randomized period of the two pivotal studies COMFORT-I and COMFORT-II, patients had a median duration of exposure to Jakavi of 10.8 months (range 0.3 to 23.5 months). The majority of patients (68.4%) were treated for at least 9 months. Of the 301 patients, 111 (36.9%) had a baseline platelet count between 100,000/mm<sup>3</sup> and 200,000/mm<sup>3</sup>, and 190 (63.1%) had a baseline platelet count >200,000/mm<sup>3</sup>.

In these clinical studies, discontinuation due to adverse events, regardless of causality was observed in 11.3% of patients.

The most frequently reported adverse drug reactions were thrombocytopenia and anaemia.

Hematological adverse reactions (any CTCAE grade; Common Terminology Criteria for Adverse Events) included anaemia (82.4%), thrombocytopenia (69.8%) and neutropenia (16.6%).

Anemia, thrombocytopenia and neutropenia are dose related effects.

The three most frequent non-hematological adverse reactions were bruising (21.6%), dizziness (15.3%) and headache (14.0%).

The three most frequent non-haematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (19.9%) and hypercholesterolaemia (16.9%).

Long term safety data from two pivotal phase 3 studies assessing 457 patients with myelofibrosis treated with ruxolitinib, including data from patients initially randomized to ruxolitinib (n=301; exposure 0.3 to 68.1 months, median exposure 33.4 months) and patients who received ruxolitinib after crossing over from control treatments (n=156; exposure: 0.5 to 59.8 months, median exposure 25.0 months): The cumulative frequency of adverse events increased proportionally to the increase in the follow-up time.

With these updated data, therapy discontinuation due to adverse events was observed in 27.4% of patients treated with ruxolitinib.

#### *Polycythemia vera*

The safety of Jakavi was assessed in 184 patients with polycythemia vera in two open-label, randomized, controlled studies, the phase 3 RESPONSE study and the phase 3b RESPONSE2 study. The adverse drug reactions listed below reflect the randomized study period (up to Week 32 for RESPONSE and up to week 28 for

RESPONSE 2) with equivalent exposure to ruxolitinib and Best Available Therapy. The median duration of exposure to Jakavi during the randomized study period was 7.85months (range 0.03 to 7.85 months).

Discontinuation for adverse events, regardless of causality, was observed in 2.2% of patients.

Hematological adverse reactions (any CTCAE grade) included anemia (40.8%) and thrombocytopenia (16.8%). Anaemia or thrombocytopenia Grade 3 and 4 were reported in respectively 1.1% or 3.3%.

The three most frequent non-haematological adverse reactions were dizziness (9.2%), constipation (8.7%), and hypertension (6.5%). The three most frequent non-haematological laboratory abnormalities (any CTCAE grade) identified as adverse reactions were raised aspartate aminotransferase (26.1%), raised alanine aminotransferase (22.3%) and hypercholesterolaemia (20.7%). These were all Grade 1 to 2 with the exception of one Grade 3 raised alanine aminotransferase event.

Long term safety was evaluated using data from 367 patients with polycythemia vera treated with ruxolitinib in two phase 3 studies including data from patients initially randomized to ruxolitinib (n=184; exposure 0.03 to 43.5 months, median exposure 18.9 months) and patients who received ruxolitinib after crossing over from control treatments (n=149; exposure: 0.2 to 33.5 months, median exposure 12.0 months): With longer exposure, the cumulative frequency of AEs increased but no new safety findings emerged. When adjusted for exposure, the AE rates were generally comparable with those observed during the initial periods of the randomized studies.

#### **Tabulated summary of adverse drug reactions from clinical trials**

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

In the clinical studies program the severity of adverse drug reactions was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE) defining Grade 1=mild, Grade 2= moderate, Grade 3=severe and Grade 4=life-threatening or disabling.

**Table 1 Reports the frequency category of adverse drug reactions reported in the phase 3 studies  
(COMFORT-I, COMFORT-II, RESPONSE, RESPONSE 2)**

<b>Adverse drug reactions and CTCAE grade<sup>3</sup></b>	<b>Frequency category for MF patients</b>	<b>Frequency category for PV patients</b>
<b>Infections and infestations</b>		
Urinary Tract infections <sup>1</sup>	Very common	Common
Pneumonia <sup>1</sup>	Common	-
Herpes zoster <sup>1</sup>	Common	Common
Tuberculosis*	Uncommon	-
<b>Blood and lymphatic system disorders</b>		
Anemia <sup>2</sup>		
CTCAE <sup>1</sup> grade 4 ( $< 6.5\text{g/dL}$ )	Very common	Uncommon
CTCAE grade 3 ( $< 8.0 - 6.5\text{g/dL}$ )	Very common	Uncommon
Any CTCAE grade	Very common	Very common
Thrombocytopenia <sup>2</sup>		
CTCAE grade 4 ( $< 25,000/\text{mm}^3$ )	Common	Uncommon

<b>Adverse drug reactions and CTCAE grade<sup>3</sup></b>	Frequency category for MF patients	Frequency category for PV patients
CTCAE grade 3 (50,000 – 25,000/mm <sup>3</sup> )	Common	Common
Any CTCAE grade	Very common	Very common
Neutropenia <sup>2</sup>		
CTCAE grade 4 (<500/mm <sup>3</sup> )	Common	-
CTCAE grade 3 (<1000 – 500/mm <sup>3</sup> )	Common	-
Any CTCAE grade	Very common	-
<b>Metabolism and nutrition disorders</b>		
Weight gain <sup>1</sup>	Very common	Common
Hypercholesterolaemia <sup>2</sup> CTCAE grade 1 and 2	Very common	Very common
Hypertriglyceridaemia <sup>2</sup> CTCAE grade 1	-	Very common
<b>Nervous system disorders</b>		
Dizziness <sup>1</sup>	Very common	Very common
Headache <sup>1</sup>	Very common	-
<b>Gastrointestinal disorders</b>		
Flatulence <sup>1</sup>	Common	-
Constipation <sup>1</sup>	-	Common
<b>Hepatobiliary disorders</b>		
Raised alanine aminotransferase <sup>2</sup>		
CTCAE grade 3 (> 5x – 20 x ULN)	Common	Uncommon
Any CTCAE grade	Very common	Very common
Raised aspartate aminotransferase <sup>2</sup>		
Any CTCAE grade	Very common	Very common
<b>Skin and subcutaneous tissue disorders</b>		
Bruising <sup>1</sup>	Very common	-
<b>Vascular disorders</b>		
Hypertension <sup>1</sup>	-	Common

<sup>1</sup> Frequency is based on adverse event data.

<sup>2</sup> Frequency is based on laboratory values.

<sup>3</sup> Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0;

Grade 1=mild, Grade 2= moderate, Grade 3=severe, Grade 4=life-threatening or disabling.

ULN = upper limit of normal

\* Frequency is based on all patients exposed to ruxolitinib in clinical trials (N=4755)

Upon discontinuation MF patients may experience a return of myelofibrosis symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In MF clinical studies the total

symptom score for myelofibrosis symptoms gradually returned to baseline values within 7 days after dose discontinuation.

### Description of selected adverse drug reactions

#### Anaemia

In phase 3 MF clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was 1.5 months. One patient (0.3%) discontinued treatment because of anaemia.

In patients receiving Jakavi mean decreases in hemoglobin reached a nadir of approximately 15 to 20 g/L below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 10 g/L below baseline. This pattern was observed in patients regardless of whether they had received transfusion during therapy.

In the randomized, placebo controlled study (COMFORT-I), 59.4% of Jakavi treated patients and 37.1% of patients receiving placebo received red blood cell transfusions during randomized treatment. In the COMFORT-II study, the rate of packed red blood cell transfusions was 51.4% in the Jakavi arm and 38.4% in the best available therapy arm (BAT).

#### Thrombocytopenia

In the Phase 3 MF clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50,000/mm<sup>3</sup> was 14 days. During the randomized period platelet transfusions were administered to 4.5% of patients receiving Jakavi and to 5.8% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in 0.7% of patients receiving Jakavi and 0.9% of patients receiving control regimens. Patients with a platelet count of 100,000/mm<sup>3</sup> to 200,000/mm<sup>3</sup> before starting Jakavi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with platelet count >200,000/mm<sup>3</sup> (64.2% versus 35.4%).

#### Neutropenia

In the phase 3 clinical studies in MF, in patients who developed Grade 3 or 4 neutropenia, the median time of onset was 12 weeks. During the randomized period of the studies dose holding or reductions due to neutropenia were reported in 1% of patients and 0.3% of patients discontinued treatment because of neutropenia.

#### Urinary tract infections

In phase 3 MF clinical studies Grade 3 or 4 urinary tract infection was reported for 1.0% of patients. Urosepsis was reported in 1.0% of patients and kidney infection in 1 patient.

## INTERACTIONS

### Agents that may alter plasma concentration of ruxolitinib

**Strong CYP3A4 inhibitors:** In healthy subjects receiving ketoconazole, a strong CYP3A4 inhibitor, at 200 mg twice daily for four days, the AUC of Jakavi increased by 91% and the half-life was prolonged from 3.7 to 6.0 hours.

When administering Jakavi with strong CYP3A4 inhibitors the total daily dose of Jakavi should be reduced by approximately 50%.

Patients should be closely monitored for cytopenias and dose titrated based on safety and efficacy (see section DOSAGE REGIMEN AND ADMINISTRATION).

**Mild or moderate CYP3A4 inhibitors:** In healthy subjects receiving erythromycin, a moderate CYP3A4 inhibitor, at 500 mg twice daily for four days, there was a 27% increase in the AUC of Jakavi.

No dose adjustment is recommended when Jakavi is co administered with mild or moderate CYP3A4 inhibitors (e.g. erythromycin). Patients should be closely monitored for cytopenias when initiating therapy with a moderate CYP3A4 inhibitor.

**Dual moderate CYP2C9 and CYP3A4 inhibitors (e.g Fluconazole):** Based on in silico modeling, AUC increase of ruxolitinib of 2.9-fold and 4.3-fold when co-administered with 200 mg or 400 mg fluconazole, respectively, is predicted. A 50% dose reduction should be considered when using medicinal products which are dual inhibitors of CYP2C9 and CYP3A4 enzymes. Avoid the concomitant use of Jakavi with fluconazole doses of greater than 200 mg daily.

**CYP3A4 inducers:** Upon initiation of a CYP3A4 inducer, no dose adjustment is recommended. Gradual dose increases of Jakavi may be considered if the effectiveness of therapy is diminished during treatment with a CYP3A4 inducer.

In healthy subjects receiving rifampin, a potent CYP3A4 inducer, at 600 mg once daily for ten days, the AUC of Jakavi following a single dose decreased by 71% and the half-life decreased from 3.3 to 1.7 hours. The relative amount of active metabolites increased in relation to parent compound.

**P-glycoprotein and other transporters:** No dose adjustment is recommended when Jakavi is co-administered with substances that interact with P-gp and other transporters.

#### **Other drug interactions studied**

##### **CYP3A4 substrates:**

A study in healthy subjects indicated that Jakavi had no clinically significant pharmacokinetic interaction with midazolam (CYP3A4 substrate).

##### **Oral contraceptives:**

A study in healthy subjects indicated that Jakavi does not affect the pharmacokinetics of an oral contraceptive containing ethinylestradiol and levonorgestrel. Therefore it is not anticipated that contraceptive efficacy of this combination will be compromised by co-administration of ruxolitinib.

### **WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, BREAST-FEEDING AND FERTILITY**

#### **Women of child-bearing potential**

Women of child-bearing potential must take appropriate precautions to avoid becoming pregnant during treatment.

In case pregnancy occurs, risk/benefit evaluations must be carried out on an individual basis with careful counseling regarding potential risk to the fetus using the most recent data available.

#### **Pregnancy**

There are no adequate and well-controlled studies of Jakavi in pregnant women.

Embryo-fetal development studies with ruxolitinib in rats and rabbits did not indicate teratogenicity. Ruxolitinib was embryotoxic and fetotoxic in rats (increases in post-implantation loss and reduced fetal weights) (see section NON-CLINICAL SAFETY DATA).

The potential risk for humans is unknown. The use of Jakavi during pregnancy is not recommended.

#### **Breast-feeding**

Women taking Jakavi should not breast-feed.

In lactating rats, ruxolitinib and/or its metabolites were excreted into the milk with a concentration that was 13-fold higher than the maternal plasma concentration. It is not known whether Jakavi is excreted in human milk.

#### **Fertility**

There are no human data on the effect of ruxolitinib on fertility. In animal studies, no effects were observed on fertility or reproductive performance of male or female rats. In a pre- and postnatal study in rats, fertility in the first generation offspring was also not affected (see section NON-CLINICAL SAFETY DATA).

## **OVERDOSAGE**

There is no known antidote for overdoses with Jakavi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given.

Hemodialysis is not expected to enhance the elimination of Jakavi.

## **CLINICAL PHARMACOLOGY**

### **Mechanism of action (MOA)**

Ruxolitinib is a selective inhibitor of the Janus Associated Kinases (JAKs) JAK1 and JAK2 ( $IC_{50}$  values of 3.3 nM and 2.8 nM for JAK1 and JAK2 enzymes, respectively). These mediate the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK-STAT pathway has been associated with several cancers and increased proliferation and survival of malignant cells.

Myelofibrosis (MF) and Polycythemia vera (PV) are myeloproliferative neoplasms (MPN) known to be associated with dysregulated JAK1 and JAK2 signaling. The basis for the dysregulation is believed to include high levels of circulating cytokines that activate the JAK-STAT pathway, gain-of function mutations such as JAK2V617F, and silencing of negative regulatory mechanisms. MF patients exhibit dysregulated JAK signaling regardless of JAK2V617F mutation status. Activating mutations in JAK2 (V617F or exon 12) are found in >95% of PV patients.

Ruxolitinib inhibits JAK-STAT signaling and cell proliferation of cytokine-dependent cellular models of hematological malignancies, as well as of Ba/F3 cells rendered cytokine-independent by expressing the JAK2V617F mutated protein, with  $IC_{50}$ 's ranging from 80-320 nM. In a mouse model of JAK2V617F-positive MPN, oral administration of ruxolitinib prevented splenomegaly, preferentially decreased JAK2V617F mutant cells in the spleen, decreased circulating inflammatory cytokines (e.g., TNF-alpha, IL-6) and resulted in significantly prolonged survival in the mice at doses that did not cause myelosuppressive effects.

### **Pharmacodynamics (PD)**

Ruxolitinib inhibits cytokine induced STAT3 phosphorylation in whole blood from healthy subjects and MF and PV patients. Ruxolitinib resulted in maximal inhibition of STAT3 phosphorylation 2 hours after dosing which returned to near baseline by 8 hours in both healthy subjects and myelofibrosis patients, indicating no accumulation of either parent or active metabolites.

Baseline elevations in inflammatory markers associated with constitutional symptoms such as TNF alpha, IL-6, and CRP in subjects with MF were decreased following treatment with ruxolitinib. Patients with myelofibrosis did not become refractory to the pharmacodynamic effects of ruxolitinib treatment over time. Similarly, patients with polycythemia vera also presented with baseline elevations in inflammatory markers and these markers were decreased following treatment with ruxolitinib.

In a thorough QT study in healthy subjects, there was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supratherapeutic dose of 200 mg indicating that ruxolitinib has no effect on cardiac repolarization.

### **Pharmacokinetics (PK)**

#### **Absorption**

Ruxolitinib is a Class 1 molecule under the Biopharmaceutical Classification System, with high permeability, high solubility and rapid dissolution characteristics. In clinical studies, ruxolitinib is rapidly absorbed after oral administration with maximal plasma concentration ( $C_{max}$ ) achieved approximately 1 hour post-dose. Based on a mass balance study in humans, oral absorption of ruxolitinib was 95% or greater. Mean ruxolitinib  $C_{max}$  and total

exposure (AUC) increased proportionally over a single dose range of 5 to 200 mg. There was no clinically relevant change in the pharmacokinetics of ruxolitinib upon administration with a high-fat meal. The mean  $C_{max}$  was moderately decreased (24%) while the mean AUC was nearly unchanged (4% increase) upon dosing with a high-fat meal.

### **Distribution**

The mean volume of distribution at steady-state is 72 L in myelofibrosis patients with an inter-subject variability of 29.4% and 75 L in polycythemia vera patients with an associated inter-subject variability of 22.6%. At clinically relevant concentrations of ruxolitinib, binding to plasma proteins *in vitro* is approximately 97%, mostly to albumin. A whole body autoradiography study in rats has shown that ruxolitinib does not penetrate the blood-brain barrier.

### **Biotransformation/metabolism**

*In vitro* studies indicate that CYP3A4 is the major enzyme responsible for metabolism of ruxolitinib. Parent compound is the predominant entity in humans representing approximately 60% of the drug-related material in circulation. Two major and active metabolites were identified in plasma of healthy subjects representing 25% and 11% of parent AUC. These metabolites have one half to one fifth of the parent JAK-related pharmacological activity. The sum total of all active metabolites contribute to 18% of the overall pharmacodynamics of ruxolitinib. At clinically relevant concentrations, ruxolitinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 and is not a potent inducer of CYP1A2, CYP2B6 or CYP3A4 based on *in vitro* studies.

### **Elimination**

Following a single oral dose of [<sup>14</sup>C]-labeled ruxolitinib in healthy adult subjects, elimination was predominately through metabolism with 74% of radioactivity excreted in urine and 22% excretion via feces. Unchanged drug accounted for less than 1% of the excreted total radioactivity. The mean elimination half-life of ruxolitinib is approximately 3 hours.

### **Linearity/non-linearity**

Dose proportionality was demonstrated in the single and multiple dose studies.

### **Special populations**

#### **Effects of age, gender, or race**

Based on studies in healthy subjects, no relevant differences in ruxolitinib pharmacokinetics were observed with regard to gender and race. In a population pharmacokinetic evaluation in myelofibrosis patients, no relationship was apparent between oral clearance and patient age or race. Clearance was 17.7 L/h in women and 22.1 L/h in men, with 39% inter-subject variability in myelofibrosis patients. Clearance was 12.7 L/h in polycythemia vera patients, with a 42% inter-subject variability, and no relationship was apparent between oral clearance and gender, patient age or race in this patient population.

### **Pediatric**

The safety and effectiveness of Jakavi in pediatric patients have not been established.

### **Renal insufficiency**

Following a single ruxolitinib dose of 25 mg, the pharmacokinetics were similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites tended to increase with increasing severity of renal impairment, and most markedly in the subjects with end stage renal disease requiring hemodialysis. Ruxolitinib is not removed by dialysis. A dose modification is recommended for patients with severe renal impairment (Clcr less than 30 mL/min). For patients with end stage renal disease a modification of the dosing schedule is recommended (see section DOSAGE REGIMEN AND ADMINISTRATION).

## **Hepatic insufficiency**

Following a single ruxolitinib dose of 25 mg in patients with varying degrees of hepatic impairment, the pharmacokinetics and pharmacodynamics of ruxolitinib were assessed. The mean AUC for ruxolitinib was increased in patients with mild, moderate and severe hepatic impairment by 87%, 28% and 65%, respectively, compared to patients with normal hepatic function and indicating no clear relationship to the degree of hepatic impairment based on Child-Pugh scores. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). A dose reduction is recommended for patients with hepatic impairment (see section DOSAGE REGIMEN AND ADMINISTRATION).

## **CLINICAL STUDIES**

### **Myelofibrosis**

Two randomized Phase 3 studies (COMFORT-I and COMFORT-II) were conducted in patients with Myelofibrosis (Primary Myelofibrosis, Post-Polyctyhemia Vera Myelofibrosis or Post-Essential Thrombocythemia-Myelofibrosis). In both studies, patients had palpable splenomegaly at least 5 cm below the costal margin and risk category of intermediate 2 (2 prognostic factors) or high risk (3 or more prognostic factors) based on the International Working Group Consensus Criteria (IWG). The prognostic factors that comprise the IWG criteria consist of age >65 years, presence of constitutional symptoms (weight loss, fever, night sweats) anemia (hemoglobin <10 g/dL), leukocytosis (history of WBC >25 X 10<sup>9</sup>/L) and circulating blasts ≥1%. The starting dose of Jakavi was based on platelet count. Patients with a platelet count between 100,000 and 200,000/mm<sup>3</sup> were started on Jakavi 15 mg twice daily and patients with a platelet count >200,000/mm<sup>3</sup> were started on Jakavi 20 mg twice daily. Doses were then individualized based upon tolerability and efficacy with maximum doses of 20 mg twice daily for patients with platelet counts between 100,000 to ≤125,000/mm<sup>3</sup>, of 10 mg twice daily for patients with platelet counts between 75,000 to ≤100,000/mm<sup>3</sup>, and of 5 mg twice daily for patients with platelet counts between 50,000 to ≤75,000/mm<sup>3</sup>.

COMFORT-I was a double-blind, randomized, placebo-controlled study in 309 patients who were refractory to or were not candidates for available therapy. Patients were dosed with Jakavi or matching placebo. The primary efficacy endpoint was proportion of subjects achieving ≥35% reduction from baseline in spleen volume at Week 24 as measured by MRI or CT.

Secondary endpoints included duration of maintenance of a ≥35% reduction from baseline in spleen volume, proportion of patients who had ≥50% reduction in total symptom score from baseline to Week 24 as measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary, change in total symptom score from baseline to Week 24 as measured by the modified MFSAF v2.0 diary and overall survival.

COMFORT-II was an open-label, randomized study in 219 patients. Patients were randomized 2:1 to Jakavi versus best available therapy. Best available therapy was selected by the investigator on a patient-by-patient basis. In the best available therapy arm, 47% of patients received hydroxyurea and 16% of patients received glucocorticoids. The primary efficacy endpoint was proportion of patients achieving ≥35% reduction from baseline in spleen volume at Week 48 as measured by MRI or CT.

A secondary endpoint in COMFORT-II was the proportion of patients achieving a ≥35% reduction of spleen volume measured by MRI or CT from baseline to Week 24. Duration of maintenance of a ≥35% reduction from baseline in responding patients was also a secondary endpoint.

In COMFORT-I, patient baseline demographics and disease characteristics were comparable between the treatment arms. The median age was 68 years with 61% of patients older than 65 years and 54% male. Fifty percent (50%) of patients had primary myelofibrosis, 31% had post-polycythemia myelofibrosis and 18% had post-essential thrombocythemia myelofibrosis. Twenty-one (21%) of patients had red blood transfusions within 8 weeks of enrollment in the study. The median platelet count was 251,000/mm<sup>3</sup>. Seventy-six percent of patients had the mutation encoding the V617F substitution present in the JAK protein. Patients had a median palpable spleen length of 16 cm. At baseline 37.4% of the patients in the Jakavi arm had Grade 1 anemia, 31.6% Grade 2 and 4.5% Grade 3, while in the placebo arm 35.8% had Grade 1, 35.1% Grade 2, 4.6% Grade 3, and 0.7% Grade 4. Grade 1 thrombocytopenia was found in 12.9 % of patients in the Jakavi arm and 13.2% in the placebo arm.

In COMFORT-II, patient baseline demographics and disease characteristics were comparable between the treatment arms. The median age was 66 years with 52% of patients older than 65 years and 57% male. Fifty-three percent (53%) of the subjects had primary myelofibrosis, 31% had post-polycythemia vera myelofibrosis, and 16% had post-essential thrombocythemia myelofibrosis. 19% of patients were considered transfusion dependent at baseline. Patients had a median palpable spleen length of 15 cm.

At baseline 34.2% of the patients in the Jakavi arm had Grade 1 anemia, 28.8% Grade 2, and 7.5% Grade 3, while in the BAT arm 37% had Grade 1, 27.4% Grade 2, 13.7% Grade 3, and 1.4% Grade 4. Thrombocytopenia of Grade 1 was found in 8.2% of patients in the Jakavi arm, and 9.6% in the BAT arm. Efficacy analyses of the primary endpoint in COMFORT-I and COMFORT-II are presented in Table 2 below. A significantly larger proportion of patients in the Jakavi group achieved a  $\geq 35\%$  reduction in spleen volume from baseline in both studies compared to placebo in COMFORT-I and best available therapy in COMFORT-II.

**Table 2 Percent of Patients with  $\geq 35\%$  Reduction from Baseline in Spleen Volume at Week 24 in COMFORT-I and at Week 48 in COMFORT-II (ITT)**

	COMFORT-I		COMFORT-II	
	Jakavi (N=155)	Placebo (N=153)	Jakavi (N=144)	Best Available Therapy (N=72)
Time Points	Week 24		Week 48	
Number (%) of Subjects with Spleen Volume Reduced by $\geq 35\%$	65 (41.9)	1 (0.7)	41 (28.5)	0
95% Confidence Intervals	34.1, 50.1	0, 3.6	21.3, 36.6	0.0, 5.0
P-value	< 0.0001		< 0.0001	

In COMFORT-I, 41.9% of patients in the Jakavi group achieved a  $\geq 35\%$  reduction in spleen volume from baseline compared with 0.7% in the placebo group at Week 24. A similar proportion of patients in the Jakavi group achieved a  $\geq 50\%$  reduction in palpable spleen length.

In COMFORT-II, 28.5% of patients in the Jakavi group achieved a  $\geq 35\%$  reduction in spleen volume from baseline compared with none (0%) in the best available therapy group at Week 48. A secondary endpoint was the proportion of patients achieving a  $\geq 35\%$  reduction of spleen volume at Week 24. A significantly larger proportion of patients in the Jakavi group 46 (31.9%) achieved a  $\geq 35\%$  reduction in spleen volume from baseline compared to no (0%) patients in the best available therapy group (p-value <0.0001).

A significantly higher proportion of patients in the Jakavi group achieved  $\geq 35\%$  reduction from baseline in spleen volume regardless of the presence or absence of the JAK2V617F mutation or the disease subtype (primary myelofibrosis, post-polycythemia vera myelofibrosis, post-essential thrombocythemia myelofibrosis).

Figure 1 shows a waterfall plot of the percent change from baseline in spleen volume at Week 24 in COMFORT-I. Among the 139 patients in the Jakavi group who had both baseline and Week 24 spleen volume evaluations, all but two patients had some level of reduction in spleen volume at Week 24, with a median reduction of 33%. Among the 106 patients in the placebo group who had both baseline and Week 24 spleen volume evaluations, there was a median increase of 8.5%.

**Figure 1 Waterfall Plot of Percent Change From Baseline in Spleen Volume at Week 24 (Observed Cases) COMFORT- I**

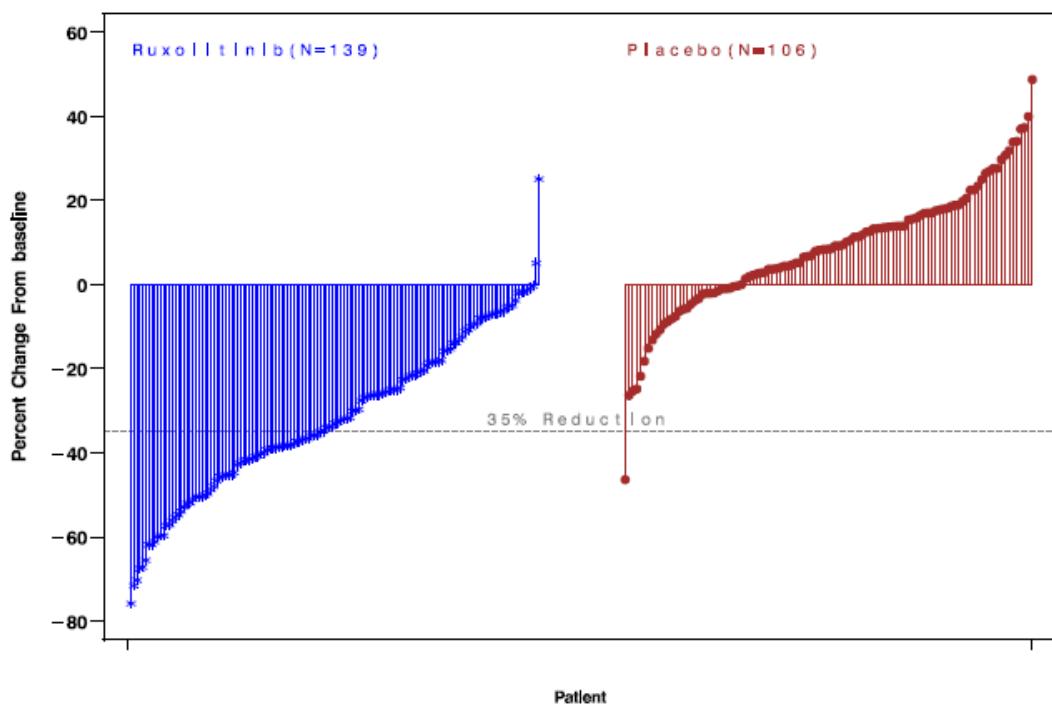
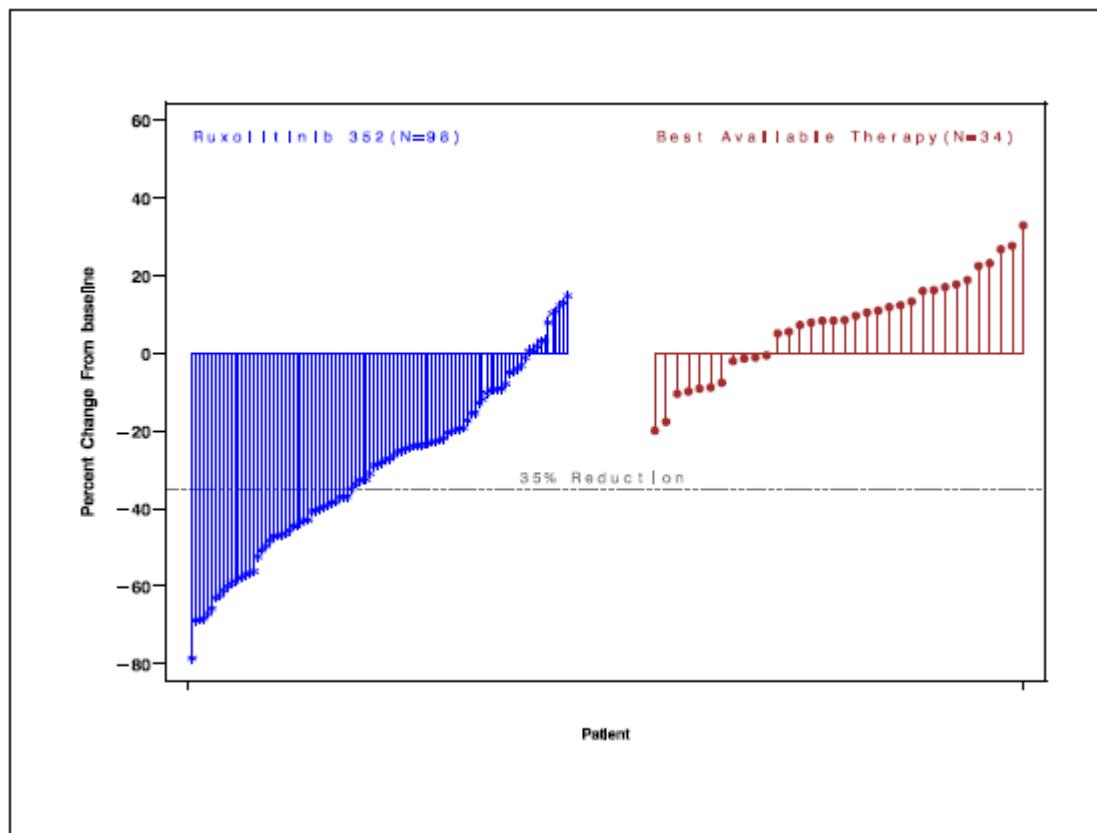


Figure 2 shows a waterfall plot of the percent change from baseline in spleen volume at Week 48 in COMFORT-II. Among the 98 patients in the Jakavi group who had both baseline and Week 48 spleen volume evaluations, the median reduction in spleen volume at Week 48 was 28%. Among the 34 patients in the Best Available Therapy group who had both baseline and Week 48 spleen volume evaluations, there was a median increase of 8.5%.

**Figure 2 Waterfall Plot of Percent Change from Baseline in Spleen Volume at Week 48 in COMFORT-II**



The probability of duration from 1st  $\geq 35\%$  reduction of spleen volume to 25% increase from nadir and loss of response in COMFORT-I and COMFORT-II is shown in Table 3 below.

**Table 3 Kaplan-Meier Analysis of Duration from 1st  $\geq 35\%$  Reduction of Spleen Volume to 25% Increase from Nadir and Loss of Response in Jakavi Patients (COMFORT- I and - II)**

Statistics	Jakavi (COMFORT-I)	Jakavi (COMFORT-II)
Probability of >12 weeks of duration (95% CI)	0.98 (0.89, 1.00)	0.92 (0.82, 0.97)
Probability of >24 weeks of duration (95% CI)	0.89 (0.75, 0.95)	0.87 (0.76, 0.93)
Probability of >36 weeks of duration (95% CI)	0.71 (0.41, 0.88)	0.77 (0.63, 0.87)
Probability of >48 weeks of duration (95% CI)	not applicable	0.52 (0.18, 0.78)

Among the 80 patients that showed a  $\geq 35\%$  reduction at any time point in COMFORT-I and of the 69 patients in COMFORT-II, the probability that a patient would maintain a response on Jakavi for at least 24 weeks was 89% and 87% in COMFORT-I and COMFORT-II respectively and the probability of maintaining a response for at least 48 weeks was 52% in COMFORT -II.

Jakavi improves myelofibrosis-related symptoms and quality of life (QOL) in patients with PMF, PPV-MF and PET-MF. In COMFORT-I symptoms of MF were captured using the modified MFSAF diary v2.0 as an electronic diary, which subjects completed daily. The change from Baseline in the Week 24 total score was a

secondary endpoint in this study. Significantly larger proportion of subjects in the Jakavi group achieved a  $\geq 50\%$  improvement from Baseline in the Week 24 total symptom score compared with the placebo group (45.9% and 5.3%, respectively,  $p < 0.0001$  using the Chi-Squared test).

An improvement in overall quality of life was measured by the EORTC QLQ-C30 in both COMFORT-COMFORT-II and I. COMFORT-I compared Jakavi to placebo at 24 weeks and COMFORT-II compared Jakavi to best available therapy at 48 weeks. At baseline for both studies, EORTC QLQ-C30 individual subscale scores for the Jakavi and comparator groups were similar. At Week 24 in COMFORT-I, the Jakavi group showed significant improvement in the global health status/quality of life of the EORTC QLQ-C30 compared with the placebo group (mean change of +12.3 and -3.4 for Jakavi and placebo, respectively,  $p < 0.0001$ ). At week 24 and week 48, the Jakavi group in COMFORT-II showed a trend towards greater improvement of global health status/quality of life compared to best available therapy, an exploratory endpoint, consistent with the COMFORT-I findings.

In COMFORT-I, after a median follow-up of 34.3 months, the death rate in patients randomized to the ruxolitinib arm was 27.1% (42 of 155 patients) versus 35.1% (54 of 154) in patients randomized to placebo. There was a 31.3% reduction in the risk of death in the ruxolitinib arm as compared to placebo (HR 0.687; 95% CI 0.459-1.029;  $p = 0.0668$ ). At final analysis, after a median follow up of 61.7 months, the reduction in risk of death was maintained at 30.7% (HR 0.693; 95% CI: 0.503, 0.956,  $p=0.025$ ).

In COMFORT-II, after a median follow-up of 34.7 months, the death rate in patients randomized to ruxolitinib was 19.9% (29 of 146 patients) versus 30.1% (22 of 73 patients) in patients randomized to best available therapy (BAT). There was a 52% reduction in risk of death in the ruxolitinib arm compared to BAT arm (HR 0.48; 95% CI 0.28-0.85;  $p = 0.009$ ). At final analysis, after a median follow up of 55.9 months, the reduction in risk of death was consistent with COMFORT I (HR 0.67, 95% CI 0.44-1.02,  $p=0.062$ ).

### **Polycythemia vera**

A randomized, open-label, active-controlled Phase 3 study (RESPONSE) was conducted in 222 patients with polycythemia vera who were resistant to or intolerant of hydroxyurea. 110 patients were randomized to the ruxolitinib arm and 112 patients to the BAT arm. The starting dose of Jakavi was 10 mg twice daily. Doses were then adjusted in individual patients based on tolerability and efficacy with a maximum dose of 25 mg twice daily. BAT was selected by the investigator on a patient-by-patient basis and included hydroxyurea (59.5%), interferon/pegylated interferon (11.7%), anagrelide (7.2%), pipobroman (1.8) and observation (15.3%).

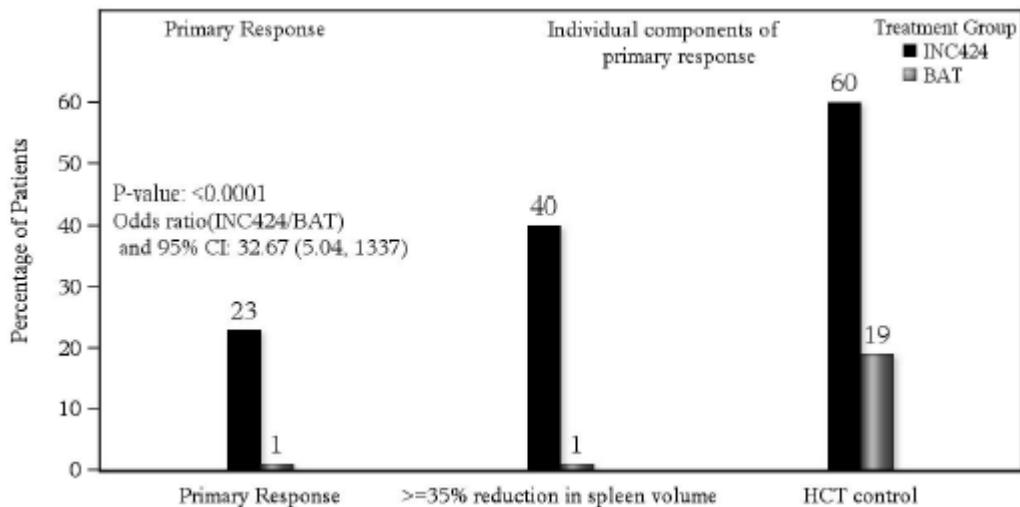
Baseline demographics and disease characteristics were comparable between the two treatments arms. The median age was 60 years (range 33 to 90 years). Patients in the ruxolitinib arm had PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately 3 years. Most patients (> 80%) had received at least two phlebotomies in the last 24 weeks prior to screening.

The primary composite endpoint was the proportion of patients achieving both the absence of phlebotomy eligibility (HCT control) and  $\geq 35\%$  reduction in spleen volume from baseline at Week 32. Phlebotomy eligibility was defined as a confirmed HCT  $> 45\%$  that is at least 3 percentage points higher than the HCT obtained at baseline or a confirmed HCT  $> 48\%$ , whichever is lower. Key secondary endpoints included the proportion of patients who achieved the primary endpoint and who remained free from progression at Week 48, and the proportion of patients achieving complete hematological remission at Week 32.

The study met its primary objective and a higher proportion of patients in the Jakavi group achieved the primary composite endpoint and each of its individual components. Significantly more patients on Jakavi (23%) compared to BAT (0.9%) achieved a primary response ( $p < 0.0001$ ). Hematocrit control was achieved in 60% of patients in the Jakavi arm compared to 18.75% in the BAT arm and  $\geq 35\%$  reduction in spleen volume was achieved in 40% of patients in the Jakavi arm compared to 0.9% in the BAT arm (Figure 3).

Both key secondary endpoints were also met: The proportion of patients achieving a complete hematologic remission was 23.6% on Jakavi compared to 8.0% on BAT ( $p=0.0013$ ), and the proportion of patients achieving a durable primary response at week 48 was 20% on Jakavi and 0.9% on BAT ( $p < 0.0001$ ).

**Figure 3: Patients achieving the primary endpoint and components of the primary endpoint at Week 32**



Symptom burden was assessed using the MPN-SAF total symptom score (TSS) electronic patient diary consisting of 14 questions. At Week 32, 49% and 64% of patients treated with ruxolitinib achieved a  $\geq 50\%$  reduction in TSS-14 and TSS-5, respectively, compared to only 5% and 11% of patients on BAT.

Treatment benefit perception was measured by the Patient Global Impression of Change (PGIC) questionnaire. 66 % of ruxolitinib-treated patients compared to 19% in BAT reported an improvement as early as 4 weeks after the start of treatment. Improvement in perception of treatment benefit was also higher in ruxolitinib-treated patients at Week 32 (78% versus 33%).

Additional analyses from the RESPONSE study to assess durability of response were conducted at Week 80 only in the Jakavi arm. In this arm, 83% of patients were still on treatment at the time of the Week 80 data cut-off. Of patients who achieved a primary response at Week 32, 80% maintained their response for at least 48 weeks after the initial response. For patients who had achieved each of the components of the primary endpoint, all patients maintained spleen response and the probability of maintaining hematocrit control for at least 80 weeks from the initial response was 89%. 69% of patients who achieved complete hematological remission at Week 32, maintained this response for at least 48 weeks.

A second randomized, open label, active-controlled phase IIIb study (RESPONSE-2) was conducted in 149 polycythemia vera patients who were resistant to or intolerant of hydroxyurea but without palpable splenomegaly. Seventy-four patients were randomized to the ruxolitinib arm and 75 patients to the BAT arm. The starting dose and dose adjustments of Jakavi and investigator-selected BAT were similar to the RESPONSE study. Baseline demographics and disease characteristics were comparable between the two treatment arms and similar to the patient population of the RESPONSE study. The primary endpoint was the proportion of patients achieving HCT control (absence of phlebotomy eligibility) at Week 28. The key secondary endpoint was the proportion of patients achieving complete hematological remission at Week 28.

RESPONSE-2 met its primary objective with a higher proportion of patients in the Jakavi arm (62.2%) compared to the BAT arm (18.7%) achieving the primary endpoint ( $p<0.0001$ ). The key secondary endpoint was also met with significantly more patients achieving a complete hematologic remission in the Jakavi arm (23.0%) compared to the BAT arm (5.3%;  $p=0.0019$ ). At week 28, the proportion of patients achieving a  $\geq 50\%$  reduction in symptom burden as measured by the MPN-SAF total symptom score was 45.3% in the Jakavi arm and 22.7% in the BAT arm.

## **NON-CLINICAL SAFETY DATA**

Ruxolitinib has been evaluated in safety pharmacology, repeat dose toxicity, genotoxicity, reproductive toxicity studies and a carcinogenicity study. Target organs associated with the pharmacological action of ruxolitinib in repeat dose studies include bone marrow, peripheral blood and lymphoid tissues. Infections generally associated with immunosuppression were noted in dogs. Adverse decreases in blood pressure along with increases in heart rate were noted in a dog telemetry study, and an adverse decrease in minute volume was noted in a respiratory study in rats. The margins (based on unbound  $C_{max}$ ) at the non-adverse effect level in the dog and rat studies were 15.7-fold and 10.4 fold greater, respectively, than the maximum human recommended 25 mg twice daily dose. No effects were noted in an evaluation of the neuropharmacologic effects of ruxolitinib.

Administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. Ruxolitinib was administered daily by oral gavage at doses from 1.5 to 75 mg/kg/day from days 7 (the human equivalent of a newborn) to 63 post-partum (pp), 15 mg/kg/day from days 14 (the human equivalent of 1 year of age) to 63 pp and 5, 15 and 60 mg/kg/day from days 21 (the human equivalent of 2 to 3 years of age) to 63 pp. Doses  $\geq$ 30 mg/kg/day (1,200 ng\*h/mL based on unbound AUC) resulted in fractures and early termination of the groups when treatment started on day 7 pp. Reduced bone growth was observed at doses  $\geq$ 5 mg/kg/day ( $\geq$ 150 ng\*h/mL based on unbound AUC) when treatment started on day 7 pp and at  $\geq$ 15 mg/kg/day ( $\geq$ 150 ng\*h/mL based on unbound AUC) when treatment started on day 14 pp or day 21 pp. Based on unbound AUC, fractures and reduced bone growth occurred at exposures 13- and 1.5- fold the exposure in adult patients at the maximum recommended dose of 25 mg BID, respectively. The effects were generally more severe when administration was initiated earlier in the postnatal period. Other than the effects on bone development, the toxicity profile in juvenile rats was comparable to that observed in adult rats.

Ruxolitinib was not teratogenic but was associated with increases in post-implantation loss and decreases in fetal weights. No effects were noted on fertility. In a pre- and post-natal development study, there were no adverse findings for fertility indices and maternal and embryofetal survival, growth, and developmental parameters. Ruxolitinib was not mutagenic or clastogenic. Ruxolitinib was not carcinogenic in the Tg.rasH2 transgenic mouse model nor in a 2-year study in rats.

## **INCOMPATIBILITIES**

Not applicable.

## **STORAGE**

See folding box.

Jakavi should not be used after the date marked "EXPIRY" on the pack.

Jakavi must be kept out of the reach and sight of children.

## **Manufacturer:**

See folding box.

## **Further information is available from:**

**Novartis Healthcare Pvt. Ltd.,**  
Gala No. 1-A & 2-A, Bldg. No. 28, Arihant Compound,  
Kopar, Purna, Tal - Bhiwandi, Dist - Thane - 421 302, India.

Information issued: India package insert dtd 14 May 18 based on International Package Leaflet (IPL) dtd 16 Apr 18

® = Registered trademark of Novartis AG, Basle, Switzerland.

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For the use of only Registered Medical Practitioners or a Hospital or a Laboratory.

## Ribociclib 200 mg Film-coated tablets

### Kryxana®

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE42

#### DESCRIPTION AND COMPOSITION

##### Pharmaceutical form(s)

Film-coated tablet 200 mg

Light greyish violet, unscored, round, curved with beveled edges, debossed with "RIC" on one side and "NVR" on the other side.

##### Active substance

Each film-coated tablet contains ribociclib succinate, equivalent to 200 mg ribocilib.

##### Excipients

Tablet core: Microcrystalline cellulose; low-substituted hydroxypropylcellulose; crospovidone (Type A); colloidal silicon dioxide; magnesium stearate.

Coating material: Polyvinyl alcohol (partially hydrolysed); titanium dioxide (E171); iron oxide black (E172); iron oxide red (E172); talc; lecithin (soy) (E322); xanthan gum.

#### INDICATIONS

Ribociclib is a kinase inhibitor indicated in combination with:

- an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer, as initial endocrine-based therapy; or

#### DOSAGE AND ADMINISTRATION

Treatment with Ribociclib should be initiated by a physician experienced in the use of anticancer therapies.

##### Dosage regimen

##### General target population

The recommended dose of Ribociclib is 600 mg (3 x 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days. Ribociclib can be taken with or without food (see section INTERACTIONS).

For dosing and administration with the aromatase inhibitor, refer to the applicable full prescribing information.

Patients should take their dose of Ribociclib and the aromatase inhibitor at approximately the same time each day, preferably in the morning.

Treatment of pre or peri-menopausal women with Ribociclib co-administration should include an LHRH agonist according to local clinical practice standards.

### Dose modifications

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption, reduction, or discontinuation of Ribociclib. If dose reduction is required, the recommended dose reduction guidelines for adverse drug reactions (ADRs) are listed in Table 1.

**Table 1 Recommended Dose Modification Guidelines for Adverse Drug Reactions**

Ribociclib		
	Dose	Number of Tablets
Starting dose	600 mg/day	3 × 200 mg tablets
First dose reduction	400 mg/day	2 × 200 mg tablets
Second dose reduction	200 mg/day*	1 × 200 mg tablet

\*If further dose reduction below 200 mg/day is required, discontinue the treatment.

Tables 2, 3, 4 and 5 summarize recommendations for dose interruption, reduction, or discontinuation of Ribociclib in the management of specific ADRs. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment (see sections WARNINGS AND PRECAUTIONS, ADVERSE DRUG REACTIONS).

**Table 2 Dose Modification and Management for Neutropenia**

Neutropenia	Grade 1 or 2 (ANC 1,000/mm <sup>3</sup> – <LLN)	Grade 3 (ANC 500 - <1,000/mm <sup>3</sup> )	Grade 3 febrile* neutropenia	Grade 4 (ANC <500/mm <sup>3</sup> )
	No dose adjustment is required.	Interrupt Ribociclib until recovery to Grade $\leq 2$ . Resume Ribociclib at the same dose level. If toxicity recurs at Grade 3, interrupt Ribociclib dose until recovery to Grade $\leq 2$ , then resume Ribociclib at the next lower dose level.	Interrupt Ribociclib until recovery of neutropenia to Grade $\leq 2$ . Resume Ribociclib at the next lower dose level.	Interrupt Ribociclib until recovery to Grade $\leq 2$ . Resume Ribociclib at the next lower dose level.
Perform Complete Blood Counts (CBC) before initiating treatment with Ribociclib. After initiating treatment with Ribociclib, monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated.				

\*Grade 3 neutropenia with a single episode of fever  $>38.3^{\circ}\text{C}$  (or) above  $38^{\circ}\text{C}$  for more than one hour and/or concurrent infection

Grading according to CTCAE Version 4.03 CTCAE=Common Terminology Criteria for Adverse Events.

**Table 3 Dose Modification and Management for Hepatobiliary toxicity**

AST and/or ALT elevations from baseline*, without	Grade 1 (>ULN – 3 x ULN)	Grade 2 (>3 to 5 x ULN)	Grade 3 (>5 to 20 x ULN)	Grade 4 (>20 x ULN)
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<b>increase in total bilirubin above 2 x ULN</b>	No dose adjustment is required.	Baseline at <Grade 2: Interrupt Ribociclib until recovery to $\leq$ baseline Grade, then resume Ribociclib at same dose level. If Grade 2 recurs, resume Ribociclib at next lower dose level. ----- Baseline at Grade 2: No dose interruption.	Interrupt Ribociclib until recovery to $\leq$ baseline Grade, then resume at next lower dose level. If Grade 3 recurs, discontinue Ribociclib.	Discontinue Ribociclib				
<b>Combined elevations in AST and/or ALT together with total bilirubin increase, in the absence of cholestasis</b>	If patients develop ALT and/or AST $>3 \times$ ULN along with total bilirubin $>2 \times$ ULN irrespective of baseline Grade, discontinue Ribociclib.							
<b>Perform Liver Function Tests (LFTs) before initiating treatment with Ribociclib.</b>								
After initiating treatment with Ribociclib, monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated.								
If Grade $\geq 2$ abnormalities are observed, more frequent monitoring is recommended.								
<i>*Baseline = prior to treatment initiation.</i>								
<i>Grading according to CTCAE Version 4.03 CTCAE=Common Terminology Criteria for Adverse Events.</i>								

**Table 4 Dose Modification and Management for QT prolongation**

<b>ECGs with QTcF <math>&gt;480</math> msec</b>	1. Interrupt the Ribociclib dose 2. If QTcF prolongation resolves to $<481$ msec, resume Ribociclib at the next lower dose level; 3. If QTcF $\geq 481$ msec recurs, interrupt the Ribociclib dose until QTcF resolves to $<481$ msec; and then resume Ribociclib at next lower dose level
<b>ECGs with QTcF <math>&gt;500</math> msec</b>	If QTcF greater than 500 msec: Interrupt Ribociclib until QTcF reaches $<481$ msec then resume Ribociclib at next lower dose level.  If QTcF interval prolongation is greater than 500 msec or shows a greater than 60 msec change from baseline in combination with Torsade de Pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue Ribociclib.
Assess ECG prior to initiation of treatment.	
After initiating treatment with Ribociclib, repeat ECG at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated.	
In case of QTcF prolongation during treatment, more frequent ECG monitoring is recommended.	

**Table 5 Dose Modification and Management for Other Toxicities\***

<b>Other toxicities</b>	<b>Grade 1 or 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
	No dose adjustment is	Interrupt Ribociclib dose	Discontinue Ribociclib.

<b>Other toxicities</b>	<b>Grade 1 or 2</b>	<b>Grade 3</b>	<b>Grade 4</b>
	required. Initiate appropriate medical therapy and monitor as clinically indicated.	until recovery to Grade $\leq 1$ , then resume Ribociclib at the same dose level.  If Grade 3 recurs, resume Ribociclib at the next lower dose level.	

*\*excluding neutropenia, hepatobiliary toxicity, and QT interval prolongation.*

*Grading according to CTCAE Version 4.03. CTCAE=Common Terminology Criteria for Adverse Events.*

Refer to the full prescribing information for the co-administered aromatase inhibitor or LHRH agonist for dose modification guidelines in the event of toxicity and other relevant safety information.

#### **Dose modification for use of Ribociclib with strong CYP3A inhibitors**

Concomitant use of Ribociclib should be avoided with strong CYP3A inhibitors and an alternative concomitant medication should be considered with low potential for CYP3A inhibition. If a strong CYP3A inhibitor must be co-administered, the Ribociclib dose should be reduced to 200 mg once daily. If the strong inhibitor is discontinued, the Ribociclib dose should be changed (after at least 5 half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor (see sections WARNINGS AND PRECAUTIONS, INTERACTIONS AND CLINICAL PHARMACOLOGY).

#### **Special populations**

##### **Renal impairment**

Based on population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild or moderate renal impairment (see section CLINICAL PHARMACOLOGY).

Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment, a starting dose of 200 mg is recommended. Ribociclib has not been studied in breast cancer patients with severe renal impairment (see section CLINICAL PHARMACOLOGY).

##### **Hepatic impairment**

Based on a hepatic impairment study in healthy subjects and non-cancer subjects with impaired hepatic function, no dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). A dose adjustment is required in patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) and the starting dose of 400 mg is recommended. Ribociclib has not been studied in breast cancer patients with moderate and severe hepatic impairment (see section CLINICAL PHARMACOLOGY).

Review the full prescribing information for the aromatase inhibitor, or the LHRH agonist for dose modifications related to hepatic impairment.

##### **Pediatric patients**

There are limited data in pediatric patients and the safety and efficacy of Ribociclib in this population has not been established.

##### **Geriatric patients (65 years of age or older)**

No dose adjustment is required in patients over 65 years of age (see section CLINICAL PHARMACOLOGY).

##### **Method of administration**

Ribociclib should be taken orally once daily at the same time every day, preferably in the morning, with or without food. If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. Ribociclib tablets should be swallowed whole (tablets should not be chewed, crushed or split prior to swallowing). Tablets that are broken, cracked, or

otherwise not intact should not be ingested.

## **CONTRAINDICATIONS**

Ribociclib is contraindicated in patients with hypersensitivity to the active substance, or to any of the excipients.

## **WARNINGS AND PRECAUTIONS**

### **Neutropenia**

In the 3 phase III clinical studies (MONALEESA-2 (A2301), MONALEESA-7 (E2301-NSAI) and MONALEESA-3 (F2301)), neutropenia was the most frequently reported adverse drug reaction (73.7%) and a Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 58.4% of patients receiving Ribociclib plus any combination in the phase III clinical studies.

Among the patients who had Grade 2, 3 or 4 neutropenia in the phase III clinical studies, the median time to Grade 2, 3 or 4 neutropenia was 16 days. The median time to resolution of Grade  $\geq 3$  (to normalization or Grade <3) was 12 days in the Ribociclib plus any combination treatment group. Severity of neutropenia is concentration dependent. Febrile neutropenia was reported in 1.4% of patients exposed to Ribociclib in the phase III clinical studies. Physicians should inform patients to promptly report any fever (see section ADVERSE DRUG REACTIONS).

A complete blood count (CBC) should be performed before initiating therapy with Ribociclib. CBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles then as clinically indicated.

Based on the severity of the neutropenia, Ribociclib may require dose interruption, reduction or discontinuation as described in Table 2 Dose Modification and Management for Neutropenia (see section DOSAGE AND ADMINISTRATION).

In patients who develop Grade 1 or 2 neutropenia, no Ribociclib dose adjustment is required. In patients who develop Grade 3 neutropenia without fever, the Ribociclib dose should be interrupted until recovery to Grade  $\leq 2$  and then Ribociclib should be resumed at the same dose level. If Grade 3 neutropenia without fever recurs, Ribociclib dose should be interrupted until recovery, then Ribociclib should be resumed at the next lower dose level.

In patients who develop Grade 3 febrile neutropenia (ANC 500 to  $<1,000/\text{mm}^3$  with a single episode of fever  $>38.3^\circ\text{C}$  (or) above  $38^\circ\text{C}$  for more than one hour and/or concurrent infection), or patients who develop Grade 4 neutropenia, Ribociclib dose should be interrupted until recovery to Grade  $\leq 2$ , then Ribociclib should be resumed at the next lower dose level.

### **Hepatobiliary toxicity**

In the phase III clinical studies, increases in transaminases were observed. Grade 3 or 4 increases in ALT (9.7% vs. 1.5%) and AST (6.7% vs. 2.1%) were reported in the Ribociclib plus any combination and placebo plus any combination arms respectively. Grade 4 increases in ALT (1.9% vs. 0.1%) and AST (1.1% vs. 0.1%) were reported in the Ribociclib plus any combination treatment and placebo plus any combination treatment arms respectively.

In the phase III clinical studies, 83.2% ( 89/107) of Grade 3 or 4 ALT or AST elevation events occurred within the first 6 months of treatment (see section ADVERSE DRUG REACTIONS). The majority of increases in ALT and AST were reported without concurrent elevations of bilirubin. Among the patients who had Grade 3 or 4 ALT/AST elevation, the median time-to-onset was 85 days for the Ribociclib plus any combination treatment group. The median time to resolution (to normalization or Grade  $\leq 2$ ) was 22 days in the Ribociclib plus any combination treatment group.

Concurrent elevations of ALT or AST greater than three times the upper limit of normal and of total bilirubin greater than two times the upper limit of normal, with normal alkaline phosphatase levels, and in the absence of cholestasis occurred in 6 patients (4 patients in Study A2301, whose levels recovered to normal within 154 days; and 2 patients in Study F2301, whose levels recovered to normal within 121 and 532 days, respectively, after discontinuation of Ribociclib. There were no such cases reported in Study E2301.

Liver function tests (LFTs) should be performed before initiating therapy with Ribociclib. The LFTs should be monitored every 2 weeks for first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated.

Based on the severity of the transaminase elevations, Ribociclib may require dose interruption, reduction, or discontinuation as described in Table 3 Dose modification and management – Hepatobiliary toxicity (see section DOSAGE AND ADMINISTRATION). Recommendations for patients who have elevated AST/ALT Grade  $\geq 3$  at baseline have not been established.

#### **QT interval prolongation**

In the phase III clinical studies, in patients with advanced or metastatic breast cancer who received the Ribociclib plus any combination partners, review of ECG data showed 14 patients (1.3%) had  $>500$  msec post-baseline QTcF value, and 59 patients (5.6%) had a  $>60$  msec QTcF interval increase from baseline. There were no reported cases of Torsade de Pointes.

In E2301 (MONALEESA-7), the observed mean QTcF increase from baseline was approximately more than 10 msec higher in the tamoxifen plus placebo subgroup compared with NSAI plus placebo subgroup, suggesting that tamoxifen had a QTcF prolongation effect which can contribute to the QTcF observed in the ribociclib plus tamoxifen group (see section Clinical pharmacology- Cardiac electrophysiology). In the placebo arm, an increase of  $>60$  msec from baseline occurred in 6/90 (6.7%) of the patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of  $>60$  msec from baseline in the QTcF interval was observed in 14/87 (16.1%) patients receiving ribociclib plus tamoxifen and in 18/245 (7.3%) of the patients receiving ribociclib plus an NSAI.

The ECG should be assessed prior to initiation of treatment. Treatment with Ribociclib should be initiated only in patients with QTcF values less than 450 msec. The ECG should be repeated at approximately Day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated.

Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorous and magnesium) should be performed prior to initiation of treatment, at the beginning of the first 6 cycles and then as clinically indicated. Any abnormality should be corrected before and during Ribociclib therapy.

Ribociclib should be avoided in patients who already have or who are at significant risk of developing QTc prolongation. This includes patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmias
- electrolyte abnormalities

Ribociclib should be avoided with medicinal products known to prolong the QTc interval and/or strong CYP3A inhibitors as this may lead to clinically meaningful prolongation of the QTcF interval (see sections DOSAGE AND ADMINISTRATION, INTERACTIONS and CLINICAL PHARMACOLOGY). Based on the findings in E2301, Ribociclib is not recommended for use in combination with tamoxifen (see section Clinical pharmacology).

Based on the observed QT prolongation during treatment, Ribociclib may require dose interruption, reduction or discontinuation as described in Table 4-4 Dose Modification and Management-QT prolongation (see sections DOSAGE AND ADMINISTRATION, ADVERSE DRUG REACTIONS and CLINICAL PHARMACOLOGY).

#### **Reproductive toxicity**

Based on animal findings and its mechanism of action, Ribociclib can cause fetal harm when administered to a pregnant woman. Women of reproductive potential should be advised to use effective contraception during therapy with Ribociclib and for at least 21 days after the last dose (see sections PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

## ADVERSE DRUG REACTIONS

### Summary of the safety profile

The overall safety profile of Ribociclib reported below is based on the pooled data set of 1065 patients who received Ribociclib in combination with endocrine therapy (N=582 in combination with aromatase inhibitor, and N=483 in combination with fulvestrant), in double blind, placebo controlled phase III clinical studies (MONALEESA-2, MONALEESA-7-NSAI arm, MONALEESA-3) in HR-positive, HER2-negative advanced or metastatic breast cancer. The median duration of exposure to Ribociclib treatment across the pooled phase III studies dataset was 16.53 months with 61.7% patients exposed for ≥12 month.

Dose reductions due to adverse events (AEs), regardless of causality occurred in 37.3% of patients receiving Ribociclib in phase III clinical studies regardless of the combination and in 3.4% of patients receiving placebo. Permanent discontinuations due to adverse events was reported in 7.0% of patients receiving Ribociclib plus any combination and 2.9% in patients receiving placebo plus any combination. The most common AEs leading to permanent discontinuation of both Ribociclib with any combination treatment partner were ALT increased (2.0%), AST increased (1.4%) and vomiting (0.8%).

In the pooled analysis of three phase III studies, on treatment deaths, were reported in 21 cases (2.0%) of patients treated with Ribociclib plus any combination vs 16 cases (2.0%) of patients treated with placebo plus any combination treatment. Excluding the most frequent cause of death disease progression, three treatment related cause of deaths were reported in patients treated with Ribociclib plus any combination treatment. Causes of death were acute respiratory distress syndrome 1 (0.1%), acute respiratory failure 1 (0.1%), and sudden death (in the setting of Grade 3 hypokalaemia and Grade 2 QT prolongation) 1 (0.1%). The most common adverse drug reactions (ADRs) across the pooled phase III studies (reported at a frequency ≥20% and for which the rate for Ribociclib exceeds the frequency for placebo) were infections, neutropenia, leukopenia, headache, cough, nausea, fatigue, diarrhoea, vomiting, constipation, alopecia and rash.

The most common Grade 3/4 ADRs in the pooled data (reported at a frequency ≥2% and for which the frequency for Ribociclib exceeds the frequency for placebo) were infections, neutropenia, leukopenia, anaemia, abnormal liver function tests, lymphopenia, hypophosphataemia, and vomiting.

### Tabulated summary of adverse drug reactions based on pooled dataset from 3 phase III clinical studies

ADRs from the phase-III clinical studies (Table 6) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

**Table 6 Adverse drug reactions based on pooled data set from 3 phase III clinical studies**

Adverse drug reactions	Ribociclib N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Ribociclib N=1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category All Grades
<b>Infections and infestations</b>					
Infections <sup>1</sup>	434 (40.8)	245 (30.0)	41 (3.8)	8 (1.0)	Very common
<b>Blood and lymphatic system disorders</b>					
Neutropenia	785 (73.7)	41 (5.0)	624 (58.6)	11 (1.3)	Very common
Leukopenia	314 (29.5)	24 (2.9)	165 (15.5)	4 (0.5)	Very common
Anaemia	200 (18.8)	51 (6.2)	30 (2.8)	12 (1.5)	Very common
Lymphopenia	95 (8.9)	18 (2.2)	56 (5.3)	5 (0.6)	Common

Adverse drug reactions	Ribociclib N=1065 n (%)	Placebo N=818 n (%)	Ribociclib N=1065 n (%)	Placebo N=818 n (%)	Frequency category
	All Grades	All Grades	Grades 3/4	Grades 3/4	All Grades
Thrombocytopenia	95 (8.9)	11 (1.3)	8 (0.8)	1 (0.1)	Common
Febrile neutropenia	15 (1.4)	2 (0.2)	15 (1.4)	2 (0.2)	Common
<b>Eye disorders</b>					
Lacrimation increased	59 (5.5)	9 (1.1)	0	0	Common
Dry eye	54 (5.1)	18 (2.2)	0	0	Common
<b>Metabolism and nutrition disorders</b>					
Decreased appetite	163 (15.3)	101 (12.3)	6 (0.6)	1 (0.1)	Very common
Hypocalcaemia	45 (4.2)	14 (1.7)	11 (1.0)	0	Common
Hypokalaemia	33 (3.1)	21 (2.6)	12 (1.1)	5 (0.6)	Common
Hypophosphataemia	34 (3.2)	11 (1.3)	22 (2.1)	7 (0.9)	Common
<b>Nervous system disorders</b>					
Headache	253 (23.8)	177 (21.6)	5 (0.5)	4 (0.5)	Very common
Dizziness	125 (11.7)	83 (10.1)	1 (0.1)	0	Very common
Vertigo	46 (4.3)	10 (1.2)	1 (0.1)	0	Common
<b>Cardiac disorders</b>					
Syncope	19 (1.8)	9 (1.1)	12 (1.1)	7 (0.9)	Common
<b>Respiratory, thoracic and mediastinal disorders</b>					
Dyspnoea	132 (12.4)	81 (9.9)	15 (1.4)	7 (0.9)	Very common
Cough	218 (20.5)	132 (16.1)	0	0	Very common
<b>Musculoskeletal and connective tissue disorders</b>					
Back pain	211 (19.8)	153 (18.7)	20 (1.9)	7 (0.9)	Very common
<b>Gastrointestinal disorders</b>					
Nausea	475 (44.6)	219 (26.8)	15 (1.4)	4 (0.5)	Very common
Diarrhoea	317 (29.8)	176 (21.5)	16 (1.5)	5 (0.6)	Very common
Vomiting	284 (26.7)	128 (15.6)	21 (2.0)	3 (0.4)	Very common
Constipation	253 (23.8)	129 (15.8)	8 (0.8)	0	Very common
Stomatitis	122 (11.5)	53 (6.5)	3 (0.3)	1 (0.1)	Very common
Abdominal pain <sup>2</sup>	182 (17.1)	107 (13.1)	14 (1.3)	4 (0.5)	Very common
Dysgeusia	71 (6.7)	36 (4.4)	1 (0.1)	0	Common
Dyspepsia	88 (8.3)	35 (4.3)	1 (0.1)	0	Common
<b>Hepatobiliary disorders</b>					
Hepatotoxicity <sup>3</sup>	19 (1.8)	7 (0.9)	15 (1.4)	4 (0.5)	Common

Adverse drug reactions	Ribociclib N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Ribociclib N=1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category All Grades
<b>Skin and subcutaneous tissue disorders</b>					
Alopecia	256 (24.0)	97 (11.9)	0	0	Very common
Rash <sup>4</sup>	227 (21.3)	70 (8.6)	10 (0.9)	0	Very common
Pruritus	177 (16.6)	48 (5.9)	3 (0.3)	0	Very common
Erythema	43 (4.0)	8 (1.0)	2 (0.2)	0	Common
Dry skin	88 (8.3)	18 (2.2)	0	0	Common
Vitiligo	16 (1.5)	0	0	0	Common
<b>General disorders and administration site conditions</b>					
Fatigue	348 (32.7)	249 (30.4)	20 (1.9)	4 (0.5)	Very common
Peripheral oedema	147 (13.8)	71 (8.7)	1 (0.1)	0	Very common
Asthenia	145 (13.6)	103 (12.6)	7 (0.7)	3 (0.4)	Very common
Pyrexia	139 (13.1)	52 (6.4)	4 (0.4)	0	Very common
Dry mouth	74 (6.9)	44 (5.4)	1 (0.1)	0	Common
Oropharyngeal pain	67 (6.3)	33 (4.0)	0	0	Common
<b>Investigations</b>					
Abnormal liver function tests <sup>5</sup>	184 (17.3)	66 (8.1)	93 (8.7)	16 (2.0)	Very common
Blood creatinine increased	67 (6.3)	15 (1.8)	4 (0.4)	0	Common
Electrocardiogram QT prolonged	69 (6.5)	13 (1.6)	13 (1.2)	2 (0.2)	Common

<sup>1</sup> Infections: Urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (<1%).

<sup>2</sup> Abdominal pain: Abdominal pain, abdominal pain upper.

<sup>3</sup> Hepatotoxicity: hepatocellular injury, drug induced liver injury, hepatotoxicity, hepatic failure, autoimmune hepatitis (single case).

<sup>4</sup> Rash: rash, rash maculopapular, rash pruritic.

<sup>5</sup> Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

### Laboratory abnormalities

Clinically relevant abnormalities of routine haematological or biochemical laboratory values from the dataset of 3 pooled phase III studies, are presented in Table 7.

**Table 7** Laboratory abnormalities based on pooled dataset from phase III clinical studies

Laboratory abnormalities	Ribociclib N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Ribociclib N= 1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category (all Grades)
<b>Hematological parameters</b>					
Leukocyte count decreased	1002 (94.1)	243 (29.7)	336 (31.5)	8 (1.0)	Very common
Neutrophil count decreased	985 (92.5)	207 (25.3)	622 (58.4)	13 (1.6)	Very common
Haemoglobin decreased	698 (65.5)	309 (37.8)	36 (3.4)	13 (1.6)	Very common
Lymphocyte count decreased	649 (60.9)	209 (25.6)	163 (15.3)	30 (3.7)	Very common
Platelet count decreased	332 (31.2)	73 (8.9)	12 (1.1)	3 (0.4)	Very common
<b>Biochemical parameters</b>					
Alanine aminotransferase increased	466 (43.8)	291 (35.6)	103 (9.7)	12 (1.5)	Very common
Aspartate aminotransferase increased	498 (46.8)	308 (37.7)	71 (6.7)	17 (2.1)	Very common
Creatinine increased	409 (38.4)	107 (13.1)	7 (0.7)	1 (0.1)	Very common
Phosphorous decreased	165 (15.5)	66 (8.1)	44 (4.1)	8 (1.0)	Very common
Potassium decreased	95 (8.9)	68 (8.3)	17 (1.6)	9 (1.1)	Common
Gamma glutamyl transferase increased	357 (48.8)	220 (45.1)	53 (7.3)	47 (9.6)	Very common
Albumin decreased	112 (10.5)	45 (5.5)	1 (0.1)	1 (0.1)	Very common
Glucose serum decreased	184 (17.3)	100 (12.2)	1 (0.1)	1 (0.1)	Very common
Bilirubin increased	54 (5.1)	44 (5.4)	9 (0.8)	9 (1.1)	Common

#### Description of selected adverse drug reactions

##### Neutropenia

Neutropenia was most frequently reported by laboratory findings in the phase III studies. Based on its severity, neutropenia was managed by laboratory monitoring, dose interruption and/or dose modification. Treatment discontinuation due to neutropenia was low (0.8%) in patients receiving Ribociclib plus any combination partner (see sections DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

##### Hepatobiliary toxicity

In the phase III clinical studies, hepatobiliary toxicity events occurred in a higher proportion of patients in the Ribociclib plus any combination arms vs the placebo plus any combination arms (23.2% vs 16.5%,

respectively), with more Grade 3/4 adverse events reported in the patients treated with Ribociclib plus any combination treatment (11.4% vs 5.4%, respectively). Dose interruptions and/or adjustments due to hepatobiliary toxicity events were reported in 10.4% of Ribociclib treated patients, primarily due to ALT increased (6.9%) and/or AST increased (6.1%). Discontinuation of treatment with Ribociclib due to abnormal liver function tests, hepatotoxicity were 2.3% and 0.4% respectively (see section WARNINGS AND PRECAUTIONS).

### QT prolongation

In the phase III clinical studies, 8.4% of patients in the Ribociclib arm and 3.2% in the placebo arm had at least one event of QT interval prolongation (including ECG QT prolonged, syncope). Dose interruptions-adjustments were reported in 2.3% of Ribociclib treated patients due to electrocardiogram QT prolonged and syncope.

A central analysis of ECG data (average of triplicate) showed 52 patients (4.9%) and 11 patients (1.4%) with at least one post-baseline QTcF >480 m sec for the Ribociclib treatment arm and the placebo arm respectively. Among the patients who had QTcF prolongation of >480 m secs, the median time to onset is 15 days, regardless of combination and these changes were reversible with dose interruption and/or dose reduction (see sections DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY).

## INTERACTIONS

Ribociclib is primarily metabolized by CYP3A and is a time-dependent inhibitor of CYP3A *in vivo*. Therefore, medicinal products which can influence CYP3A enzyme activity may alter the pharmacokinetics of ribociclib.

### Medicinal products that may increase ribociclib plasma concentrations

Co-administration of a strong CYP3A4 inhibitor (ritonavir) increased ribociclib exposure in healthy subjects by 3.21-fold. Concomitant use of strong CYP3A inhibitors including but not limited to clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole (see section WARNINGS AND PRECAUTIONS) should be avoided. Alternative concomitant medications with low potential to inhibit CYP3A should be considered and patients should be monitored for ADRs (see sections DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY).

If co-administration of Ribociclib with a strong CYP3A inhibitor cannot be avoided, Ribociclib dose should be reduced to 200 mg. However, there are no clinical data with this dose adjustment (see section DOSAGE AND ADMINISTRATION). If the strong inhibitor is discontinued, the Ribociclib dose should be resumed (after at least 5 half-lives of the CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring for ADRs is recommended. In the event of Ribociclib related toxicity, dose should be modified (see section DOSAGE AND ADMINISTRATION), or treatment should be interrupted until toxicity is resolved (see sections DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY)

Patients should be instructed to avoid grapefruits or grapefruit juice, all of which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib.

### Medicinal products that may decrease ribociclib plasma concentrations

Co-administration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89%. Avoid concomitant use of strong CYP3A inducers, including but not limited to phenytoin, rifampin, carbamazepine and St John's Wort (*Hypericum perforatum*). An alternate concomitant medication with no or minimal potential to induce CYP3A should be considered (see sections WARNINGS AND PRECAUTIONS and CLINICAL PHARMACOLOGY).

### Medicinal products that may have their plasma concentrations altered by ribociclib

Co-administration of midazolam (CYP3A4 substrate) with multiple doses of Ribociclib (400 mg) increased the midazolam exposure by 280% (3.80-fold) in healthy subjects, compared with administration of midazolam alone. Simulations using physiologically-based PK (PBPK) models suggested that Ribociclib given at the clinically relevant dose of 600 mg is expected to increase the midazolam AUC by 5.2-fold. Therefore caution is recommended when Ribociclib is administered with CYP3A substrates with a narrow therapeutic index. The

dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus and tacrolimus, may need to be reduced as ribociclib has the potential to increase their exposure (see section CLINICAL PHARMACOLOGY).

Co-administration of caffeine (CYP1A2 substrate) with multiple doses of Ribociclib (400 mg) increased caffeine exposure by 20% (1.20-fold) in healthy subjects, compared with administration of caffeine alone. At the clinically relevant dose of 600 mg, simulations using PBPK models predicted only weak inhibitory effects of ribociclib on CYP1A2 substrates (<2-fold increase in AUC) (see section CLINICAL PHARMACOLOGY).

#### **Medicinal products that are substrates of transporters**

*In vitro* evaluations indicated that ribociclib has a low potential to inhibit the activities of drug transporters P-gp, OAT1/3, OATP1B1/B3, and OCT1 at clinically relevant concentrations. Ribociclib may inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations (see section CLINICAL PHARMACOLOGY).

#### **Drug-food interactions**

Ribociclib can be administered with or without food (see section DOSAGE AND METHOD OF ADMINISTRATION).

Compared to the fasted state, oral administration of a single 600 mg dose of Ribociclib film-coated tablet with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib ( $C_{max}$  GMR: 1.00; 90% CI: 0.898, 1.11;  $AUC_{inf}$  GMR: 1.06; 90% CI: 1.01, 1.12 (see section CLINICAL PHARMACOLOGY).

#### **Gastric pH elevating medications**

Ribociclib exhibits high solubility at or below pH 4.5 and in bio-relevant media (at pH 5.0 and 6.5). Co-administration of Ribociclib with medicinal products that elevate the gastric pH was not evaluated in a clinical trial; however, altered ribociclib absorption was not observed in the population pharmacokinetic analysis nor in simulations using PBPK models (see section CLINICAL PHARMACOLOGY).

#### **Anticipated interactions**

**Anti-arrhythmic medicines and other medicinal products that may prolong the QT interval:** Co-administration of Ribociclib should be avoided with medicinal products with known potential to prolong the QT interval such as anti-arrhythmic medicines. Concomitant use of anti-arrhythmic medicines (including but not limited to amiodarone, disopyramide, procainamide, quinidine, and sotalol), other medicinal products that are known to prolong the QT interval, including but not limited to, chloroquine, halofantrine, clarithromycin, ciprofloxacin, levofloxacin, azithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and ondansetron (i.v), should be avoided (see section WARNINGS AND PRECAUTIONS). Ribociclib is not recommended for use in combination with tamoxifen (see section WARNINGS AND PRECAUTIONS).

### **PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL**

#### **Pregnancy**

##### **Risk summary**

Based on animal data and its mechanism of action, it is possible that Ribociclib can cause fetal harm when administered to a pregnant woman.

The patient should be advised of the risk to a fetus, if Ribociclib is used during pregnancy or if the patient becomes pregnant while taking this medicinal product.

There are no adequate and well-controlled studies in pregnant women. Reproductive studies in rats and rabbits have demonstrated ribociclib induced embryotoxicity, fetotoxicity and teratogenicity. Following prenatal exposure, increased incidences of post-implantation loss and reduced fetal weights were observed in rats and ribociclib was teratogenic in rabbits as evidenced by increased incidences of fetal abnormalities (malformations and external, visceral and skeletal variants) at exposures lower than or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC. There are no available human data informing the drug-associated risk.

## **Data**

### **Animal Data**

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1,000 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis.

In rats, 1,000 mg/kg/day was lethal in the maternal animals. At 300 mg/kg/day, a slight, non-adverse trend towards reduced maternal body weight gain and fetal toxicity evidenced by reduced fetal weights accompanied by skeletal changes were considered to be transitory and/or related to the lower fetal weights. There were no effects upon embryo-fetal mortality or adverse effects on fetal morphology at 50 or 300 mg/kg/day. The no-observed-adverse-effect level (NOAEL) for maternal toxicity was considered to be 300 mg/kg/day. The no-observed-effect-level (NOEL) for embryo-fetal development was considered to be 50 mg/kg/day.

In rabbits at doses  $\geq$ 30 mg/kg/day, there were adverse effects on embryo-fetal development as evidenced by increased incidences of fetal abnormalities (malformations and external, visceral and skeletal variants) and fetal growth (lower fetal weights). These findings included reduced/small lung lobes and additional vessel on the aortic arch and diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes and reduced/small accessory lung lobe (30 and 60 mg/kg), extra/rudimentary 13<sup>th</sup> ribs and misshapen hyoid bone and reduced number of phalanges in the pollex. There was no evidence of embryo-fetal mortality. The no-observed-effect level (NOEL) for maternal toxicity was considered to be at least 30 mg/kg/day and the NOEL for the embryo-fetal development was 10 mg/kg/day.

At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposure (AUC) were 13,800 ng\*hr/mL and 36,700 ng\*hr/mL, lower than or at 1.5 times, the one achieved in patients at the highest recommended dose of 600 mg/day.

## **Lactation**

### **Risk summary**

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breastfed child or the effects of ribociclib on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in nursing infants from Ribociclib, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is recommended that women taking Ribociclib should not breastfeed for at least 21 days after the last dose.

## **Data**

### **Animal data**

In lactating rats administered a single dose of 50 mg/kg, exposure to ribociclib was 3.56 fold higher in milk than in maternal plasma.

### **Females and males of reproductive potential**

Based on animal studies, Ribociclib can cause fetal harm when administered to a pregnant woman (see section NON CLINICAL SAFETY DATA).

### **Pregnancy testing**

For females of reproductive potential the pregnancy status should be verified prior to initiating treatment with Ribociclib.

### **Contraception**

Females of reproductive potential should be advised that animal studies have been performed showing ribociclib to be harmful to the developing fetus. Sexually active females of reproductive potential should use effective contraception (methods that result in < 1 % pregnancy rates) when using Ribociclib during treatment and for 21 days after stopping treatment with Ribociclib.

### **Infertility**

In a fertility study in female rats, ribociclib did not affect the reproductive function, fertility or early embryonic development at any dose up to 300 mg/kg/day (likely at an exposure lower than or equal to patients clinical exposure, at the highest recommended dose of 600 mg/day based on AUC).

A fertility study in male rats has not been performed, however atrophic changes in testes were reported in repeated dose toxicity studies in rats and dogs at exposures that were less or equal to the human exposure at the highest recommended daily dose of 600 mg/day based on AUC (see section NON CLINICAL SAFETY DATA). There are no clinical data available regarding the effects of Ribociclib on fertility. Based on animal studies, Ribociclib may impair fertility in males of reproductive potential.

## OVERDOSAGE

There is limited experience with reported cases of Ribociclib overdose in humans. General symptomatic and supportive measures should be initiated in all cases of overdosage where necessary.

## CLINICAL PHARMACOLOGY

### Mechanism of action (MOA)

Ribociclib is a selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signaling pathways which lead to cell cycle progression and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).

*In vitro*, ribociclib decreased pRb phosphorylation leading to arrest in the G1 phase of the cell cycle and reduced cell proliferation in breast cancer cell lines. *In vivo*, treatment with single agent ribociclib led to tumor regressions which correlated with inhibition of pRb phosphorylation at well tolerated doses.

*In vivo* studies using patient-derived estrogen positive breast cancer xenograft models combination of ribociclib and antiestrogens (i.e. letrozole) resulted in superior inhibition of tumor growth compared to each drug alone. Tumor regrowth was delayed for 33 days after stopping dosing.

### Pharmacodynamics (PD)

Ribociclib inhibits the CDK4/cyclin-D1 and CDK6/cyclin-D3 enzyme complexes with concentration resulting in 50% inhibition ( $IC_{50}$ ) values of 0.01 (4.3 ng/mL) and 0.039 micro molar (16.9 ng/mL) in biochemical assays, respectively.

In cell-based assays, ribociclib inhibits CDK4/6-dependent pRb phosphorylation with an average  $IC_{50}$  of 0.06 micro molar (26 ng/mL). Ribociclib halts G1 to S phase cell cycle progression measured by flow cytometry with an average  $IC_{50}$  of 0.11 micro molar (47.8 ng/mL). Ribociclib also inhibits cellular proliferation measured by bromodeoxyuridine (BrdU) uptake with an  $IC_{50}$  of 0.8 micro molar (34.8 ng/mL). The similar  $IC_{50}$  values obtained from the target modulation, cell cycle and proliferation assays confirms that the blockade of the pRb phosphorylation by ribociclib directly leads to G1 to S phase arrest and subsequent inhibition of cellular proliferation. When tested in a panel of breast cancer cell lines with known ER status, ribociclib demonstrated to be more efficacious in ER+ breast cancer cell lines than in the ER- ones.

### Cardiac electrophysiology

Serial, triplicate ECGs were collected following a single dose and at steady-state to evaluate the effect of ribociclib on the QTc interval in patients with advanced cancer. A pharmacokinetic-pharmacodynamic analysis included a total of 997 patients treated with ribociclib at doses ranging from 50 to 1,200 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval.

### Pharmacokinetics (PK)

The pharmacokinetics of ribociclib were investigated in patients with advanced cancer following oral daily doses of 50 mg to 1,200 mg. Healthy subjects received single oral doses ranging of 400 or 600 mg or repeated daily oral doses (8 days) of 400 mg.

### Absorption

Following oral administration of Ribociclib to patients with advanced solid tumors or lymphomas peak plasma levels ( $C_{max}$ ) of ribociclib were achieved between 1 and 4 hours (time to reach maximum concentration,  $T_{max}$ ). Ribociclib exhibited slightly over-proportional increases in exposure ( $C_{max}$  and AUC) across the dose range

tested (50 to 1,200 mg). Following repeated once daily dosing, steady-state was generally achieved after 8 days and ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range: 0.972 to 6.40).

#### **Food effect:**

Compared to the fasted state, oral administration of a single 600 mg dose of ribociclib film-coated tablet formulation with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib ( $C_{max}$  GMR: 1.00; 90% CI: 0.898, 1.11;  $AUC_{inf}$  GMR: 1.06; 90% CI: 1.01, 1.12) (see section INTERACTIONS).

#### **Distribution**

Binding of ribociclib to human plasma proteins *in vitro* was approximately 70% and independent of concentration (10 to 10,000 ng/mL). Ribociclib was equally distributed between red blood cells and plasma with a mean *in vivo* blood-to-plasma ratio of 1.04. The apparent volume of distribution at steady-state ( $V_{ss}/F$ ) was 1,090 L based on the population pharmacokinetic analysis.

#### **Biotransformation/metabolism**

*In vitro* and *in vivo* studies indicated ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600 mg dose of [ $^{14}C$ ]ribociclib to humans, the primary metabolic pathways for ribociclib involved oxidation (dealkylation, C and/or N-oxygenation, oxidation (-2H)) and combinations thereof. Phase II conjugates of ribociclib phase I metabolites involved N-acetylation, sulfation, cysteine conjugation, glycosylation and glucuronidation. Ribociclib was the major circulating drug-derived entity in plasma (43.5%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide), each representing an estimated 9.39%, 8.60%, and 7.78% of total radioactivity, and 21.6%, 19.8%, and 17.9% of ribociclib exposure, respectively. Clinical activity (pharmacological and safety) of ribociclib was primarily due to parent drug, with negligible contribution from circulating metabolites.

Ribociclib was extensively metabolized with the unchanged drug accounting for 17.3% and 12.1% in feces and urine, respectively. Metabolite LEQ803 was a significant metabolite in excreta and represented approximately 13.9% and 3.74% of the administered dose in feces and urine, respectively. Numerous other metabolites were detected in both feces and urine in minor amounts ( $\leq 2.78\%$  of the administered dose).

#### **Elimination**

The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance ( $CL/F$ ) was 25.5 L/hr (66% CV) at steady-state at 600 mg in patients with advanced cancer. The geometric mean plasma terminal half-life ( $T_{1/2}$ ) of ribociclib ranged from 29.7 to 54.7 hours and the geometric mean  $CL/F$  of ribociclib ranged from 39.9 to 77.5 L/hr at 600 mg across studies in healthy subjects.

Ribociclib is eliminated mainly via the feces, with a small contribution from the renal route. In 6 healthy male subjects, following a single oral dose of [ $^{14}C$ ] ribociclib, 91.7% of the total administered radioactive dose was recovered within 21 days; feces was the major route of excretion (69.1%), with 22.6% of the dose recovered in the urine.

#### **Linearity/non-linearity**

Ribociclib exhibited slightly over-proportional increases in exposure ( $C_{max}$  and  $AUC$ ) across the dose range of 50 mg to 1,200 mg following both single dose and repeated doses. This analysis is limited by the small sample sizes for most of the dose cohorts with a majority of the data coming from the 600 mg dose cohort.

#### **Special populations**

##### **Renal impairment**

No dose adjustment is necessary in patients with mild or moderate renal impairment. Based on a population pharmacokinetic analysis that included 438 patients with normal renal function (eGFR  $\geq 90$  mL/min/1.73 m $^2$ ), 488 patients with mild renal impairment (eGFR 60 to <90 mL/min/1.73 m $^2$ ) and 113 patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m $^2$ ), mild and moderate renal impairment had no effect on the exposure of ribociclib (see section DOSAGE AND ADMINISTRATION).

The effect of renal impairment on the pharmacokinetics of ribociclib was also assessed in a renal impairment study that included 7 subjects with normal renal function (eGFR  $\geq$ 90 mL/min/1.73 m<sup>2</sup>), 7 subjects with severe renal impairment (eGFR 15 to <30 mL/min/1.73 m<sup>2</sup>), and 3 subjects with end stage renal disease (ESRD) (eGFR <15 mL/min/1.73 m<sup>2</sup>) at single ribociclib dose of 400 mg/day. The geometric mean AUC<sub>inf</sub> (geometric %CV, n) of 5570 ng\*hr/mL (22.8%, 7), 10900 ng\*hr/mL (38.1%, 7), 13600 ng\*hr/mL (20.9%, 3) and Cmax (geometric %CV, n) of 356 ng/mL (15%, 7), 538 ng/mL (43.3%, 7), 593 ng/mL (11.3%, 3) was observed in subjects with normal renal function, severe renal impairment and ESRD, respectively . In subjects with severe renal impairment AUC<sub>inf</sub> increased by 1.96 fold, and C<sub>max</sub> increased by 1.51 fold compared to subjects with normal renal function.

Based on this study, a starting dose of 200 mg is recommended for patients with severe renal impairment (see section 4 Dosage and administration).

### Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A); a dose adjustment is required in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) and a starting dose of 400 mg is recommended (see section DOSAGE AND ADMINISTRATION). Based on a pharmacokinetic trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib (see section DOSAGE AND ADMINISTRATION). The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.44 for C<sub>max</sub>; 1.28 for AUC<sub>inf</sub>) and severe (GMR: 1.32 for C<sub>max</sub>; 1.29 for AUC<sub>inf</sub>) hepatic impairment. Based on a population pharmacokinetic analysis that included 160 patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib, further supporting the findings from the dedicated hepatic impairment study (see section DOSAGE AND ADMINISTRATION).

### Effect of age, weight, gender and race

The population pharmacokinetic analysis showed that there are no clinically relevant effects of age, body weight, gender, or race on the systemic exposure of ribociclib that would require a dose adjustment.

### Geriatric use

Of 334 patients who received Ribociclib in the phase III study (MONALEESA 2, in ribocilin plus letrozole arm), 150 patients (44.9%) were  $\geq$ 65 years of age and 35 patients (10.5%) were  $\geq$ 75 years of age. No overall differences in safety or effectiveness of Ribociclib were observed between these patients and younger patients (see section DOSAGE AND ADMINISTRATION).

### Interactions

**Strong CYP3A inhibitors:** A drug interaction study in healthy subjects was conducted with ritonavir (strong CYP3A inhibitor). Compared to ribociclib alone, ritonavir (100 mg b.i.d for 14 days) increased ribociclib C<sub>max</sub> and AUC<sub>inf</sub> by 1.7-fold and 3.2-fold, respectively, following a single 400 mg ribociclib dose. C<sub>max</sub> and AUC<sub>last</sub> for LEQ803 (a prominent metabolite of ribociclib, accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively. Simulations using physiologically-based pharmacokinetic modeling (PBPK) suggested that a moderate CYP3A4 inhibitor (erythromycin) may increase C<sub>max</sub> and AUC of ribociclib 400 mg single dose by 1.3-fold and 1.9-fold, respectively (see sections DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS and INTERACTIONS).

**Strong CYP3A inducers:** A drug interaction study in healthy subjects was conducted with rifampicin (strong CYP3A4 inducer). Compared to ribociclib alone, rifampicin (600 mg daily for 14 days) decreased ribociclib C<sub>max</sub> and AUC<sub>inf</sub> by 81% and 89%, respectively, following a single 600 mg ribociclib dose. LEQ803 C<sub>max</sub> increased 1.7-fold and AUC<sub>inf</sub> decreased by 27%, respectively. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease ribociclib single dose C<sub>max</sub> and AUC by 37% and 60%, respectively (see section INTERACTIONS).

**Cytochrome P450 enzymes (CYP3A4 and CYP1A2 substrates):** A drug interaction study in healthy subjects was conducted as a cocktail study with midazolam (sensitive CYP3A4 substrate) and caffeine (sensitive CYP1A2 substrate). Compared to midazolam and caffeine alone, multiple doses of ribociclib (400 mg once daily for 8 days) increased midazolam C<sub>max</sub> and AUC<sub>inf</sub> by 2.1-fold and 3.8-fold, respectively. Simulations using PBPK suggested that at a 600 mg ribociclib dose, midazolam C<sub>max</sub> and AUC may increase 2.4-fold and 5.2-fold, respectively. The effect of multiple doses of ribociclib on caffeine was minimal, with C<sub>max</sub> decreasing by 10%

and AUC<sub>inf</sub> increasing slightly by 20%. Simulations using PBPK suggested only weak inhibitory effects on CYP1A2 substrates at a 600 mg ribociclib dose (see section INTERACTIONS).

Ribociclib exhibited no capacity to inhibit CYP2E1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, and showed no apparent time-dependent inhibition of CYP1A2, CYP2C9, and CYP2D6 at clinically relevant concentrations. No induction of CYP1A2, CYP2B6, CYP2C9 or CYP3A4 was observed *in vitro* at clinically relevant concentrations (see section INTERACTIONS).

**Gastric pH-elevating agents:** Ribociclib exhibits high solubility at or below pH 4.5 and in bio-relevant media (at pH 5.0 and 6.5). Co-administration of ribociclib with medicinal products that elevate the gastric pH was not evaluated in a clinical trial; however, altered ribociclib absorption was not observed in population pharmacokinetic analysis nor in simulations using PBPK models (see sections DOSAGE AND ADMINISTRATION AND INTERACTIONS).

**Letrozole:** Data from clinical trials in patients with breast cancer and population PK analysis indicated no drug interaction between ribociclib and letrozole following co-administration of the drugs (see section INTERACTIONS).

**Exemestane:** Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and exemestane following coadministration of the drugs

**Anastrozole:** Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and anastrazole following coadministration of the drugs.

**Tamoxifen:** Data from a clinical trial in patients with breast cancer indicated that tamoxifen exposure was increased approximately 2 fold following coadministration of ribociclib and tamoxifen.

**Effect of ribociclib on transporters:** *In vitro* evaluations indicated that Ribociclib has a low potential to inhibit the activities of drug transporters P-gp, OATP1B1/B3, OCT1, MATE2K at clinically relevant concentrations. Ribociclib may inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations (see section INTERACTIONS).

**Effect of transporters on ribociclib:** Based on *in vitro* data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of ribociclib at therapeutic doses. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1/1B3 or OCT-1 *in vitro* (see section INTERACTIONS).

## CLINICAL STUDIES

### Study CLEE011A2301

Ribociclib was evaluated in a randomized, double-blind, placebo-controlled, multicenter phase III clinical study in the treatment of postmenopausal women with HR positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease in combination with letrozole versus letrozole alone.

A total of 668 patients were randomized in a 1:1 ratio to receive either Ribociclib 600 mg and letrozole (n= 334) or placebo and letrozole (n= 334), stratified according to the presence of liver and/or lung metastases [Yes (n=292 (44%)) vs No [n=376 (56%)]. Demographics and baseline disease characteristics were balanced and comparable between study arms. Ribociclib was given orally at a dose of 600 mg daily for 21 consecutive days followed by 7 days off treatment in combination with letrozole 2.5 mg once daily for 28 days. Patients were not allowed to cross over from placebo to Ribociclib during the study or after disease progression.

Patients enrolled in this study had a median age of 62 years (range 23 to 91). 44.2% patients were of age 65 years and older including 69 patients (10.3%) of age 75 years and older. The patients included were Caucasian (82.2%), Asians (7.6%), and Black (2.5%). All patients had an ECOG performance status of 0 or 1. A total of 43.6% of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 51.8% had received antihormonal therapy in the neo/adjuvant setting prior to study entry. 34.1% of patients had de novo metastatic disease. 20.7% of patients had bone only disease and 59.0% of patients had visceral disease.

The primary endpoint for the study was met at the planned interim analysis conducted after observing 80% of targeted progression-free survival (PFS) events using Response Evaluation Criteria in Solid Tumors (RECIST v1.1), based on the investigator assessment in the full population (all randomized patients) and confirmed by a blinded independent central radiological assessment.

The efficacy results (29 January 2016 cut-off) demonstrated a statistically significant improvement in PFS in patients receiving Ribociclib plus letrozole compared to patients receiving placebo plus letrozole in the full analysis set (hazard ratio [HR] = 0.556 with 95% CI: 0.429, 0.720, one sided stratified log-rank test p-value 0.00000329), with an estimated 44% reduction in risk of progression for patients treated with the combination of reduction in Ribociclib plus letrozole. The median PFS was not reached in the Ribociclib plus letrozole arm (95% CI: 19.3 – NE) at the time of primary analysis. The median PFS was 14.7 months (95% CI, 13.0, and 16.5) for placebo plus letrozole arm. Results were consistent across the subgroups of age, race, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, bone only metastasis disease.

Progression free survival is summarized in Table 8 and the Kaplan-Meier curve for PFS is provided in Figure 1. The results for PFS based on the blinded independent central radiological assessment were consistent with the primary efficacy results based on the investigator's assessment (hazard ratio: 0.592 with 95% CI: (0.412, 0.852). The one-sided stratified log-rank test p-value was 0.002.

The global health status/QoL showed no relevant difference between the Ribociclib plus letrozole arm and the placebo plus letrozole control arm.

Overall survival (OS) was a key secondary endpoint. At the time of primary PFS analysis, overall survival was not mature with 11% of events.

A more mature update of efficacy data (02 January 2017 cutoff) is provided in Table 9. Median PFS was 25.3 months (95% CI: 23.0, 30.3) for ribociclib plus letrozole treated patients and 16.0 months (95% CI: 13.4, 18.2) for patients receiving placebo plus letrozole. 54.7% of patients receiving ribociclib plus letrozole were estimated to be progression free at 24 months compared with 35.9% in the placebo plus letrozole arm. There was no statistically significant difference in overall survival (OS) between the Ribociclib plus letrozole arm and the placebo plus letrozole arm (HR 0.746 [95% CI 0.517, 1.078]). OS data remain immature.

Hazard ratios based on pre-specified subgroup analysis (29 January 2016 cut-off) are in favor of the Ribociclib plus letrozole arm, demonstrating that patients benefit independent of age, race, prior adjuvant/ neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone only metastasis disease.

**Table 8 CLEE011A2301 primary efficacy results (PFS) based on Investigator radiological assessment (29 January 2016 cut-off)**

	Ribociclib plus letrozole N=334	Placebo plus letrozole N=334
<b>Progression free survival</b>		
Median PFS [months] (95% CI)	NE (19.3 – NE)	14.7 (13.0 – 16.5)
Hazard ratio (95% CI)	0.556 (0.429 to 0.720)	
p-value <sup>a</sup>		0.00000329

*CI=confidence interval; N=number of patients; NE = Not estimable.*

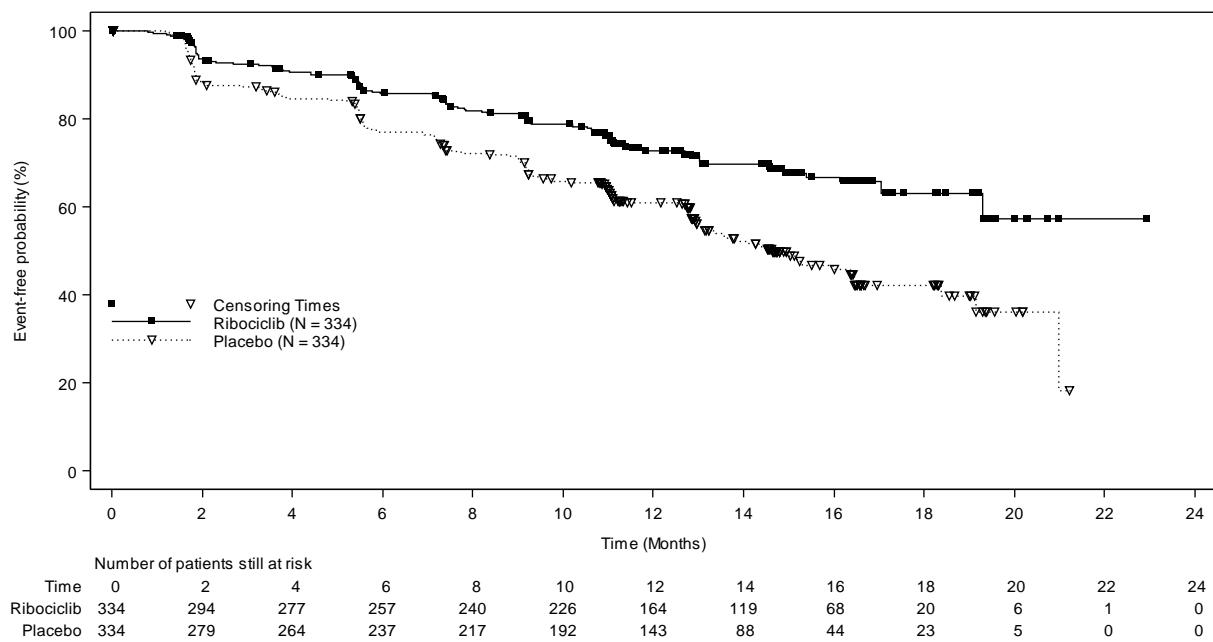
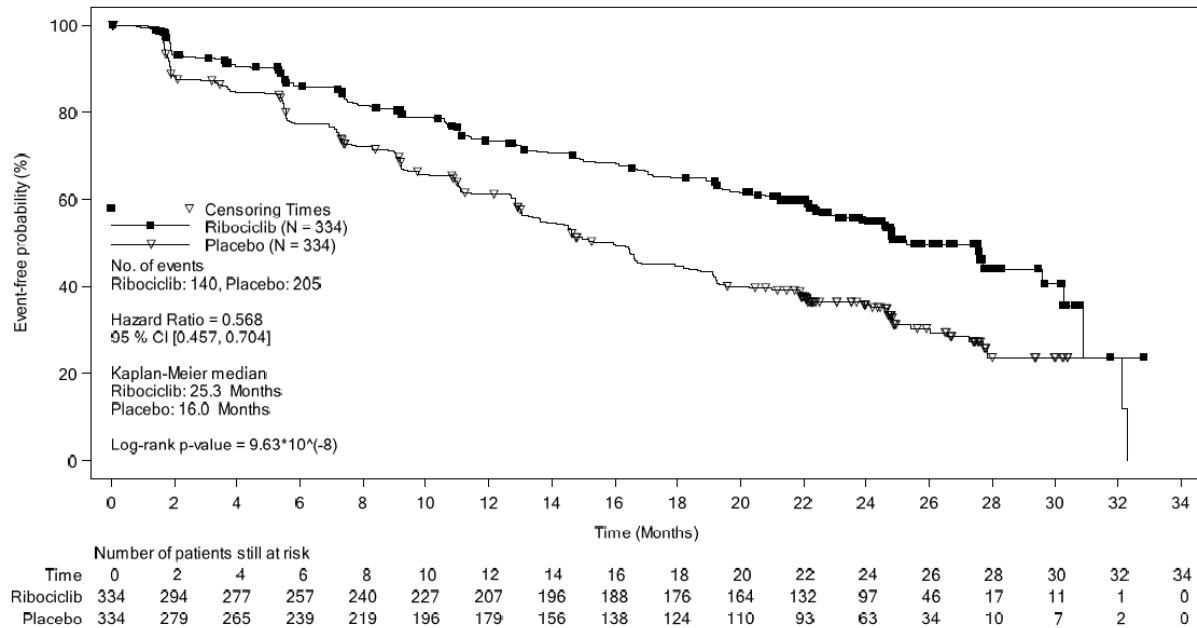
<sup>a</sup> p-value is obtained from the one-sided stratified log-rank test.

**Table 9 CLEE011A2301 primary efficacy results (PFS) based on investigator radiological assessment (02 January 2017 cut-off)**

	Ribociclib plus letrozole N=334	Placebo plus letrozole N=334
<b>Progression free survival</b>		
Median PFS [months] (95% CI)	25.3 (23.0-30.3)	16.0 (13.4-18.2)
Hazard ratio (95% CI)	0.568 (0.457-0.704)	
p-value <sup>a</sup>		9.63×10 <sup>-8</sup>

*CI=confidence interval; N=number of patients;*

<sup>a</sup>p-value is obtained from the one-sided stratified log-rank test.

**Figure 1****Kaplan-Meier plot of PFS based on Investigator review – Study A2301 (Full analysis set) (29 January 2016 cut-off)****Figure 2****Kaplan-Meier plot of PFS based on Investigator assessment – Study A2301 (Full analysis set 02 January 2017 cut-off)**

Other secondary endpoints included overall response rate (ORR), time to deterioration of ECOG performance status, safety and tolerability and change in patient-reported outcomes (PROs) for health related quality of life. In full analysis set (FAS), the overall response rate according to local radiologist assessment was 40.7% of patients (95% CI: 35.4%, 46.0%) in the Ribociclib plus letrozole arm and 27.5% (95% CI: 22.8%, 32.3%) in the placebo plus letrozole arm ( $p=0.000155$ ) the clinical benefit rate (CBR) was 79.6% of patients (95% CI: 75.3%,

84.0%) in the Ribociclib plus letrozole arm and 72.8% (95% CI: 68.0%, 77.5%) in the placebo plus letrozole arm ( $p=0.018$ ). In patients with measurable disease, the overall response rate according to local radiologists assessment was 52.7% of patients (95% CI: 46.6%, 58.9%) in the Ribociclib plus letrozole and 37.1% (95% CI: 31.1%, 43.2%) in the placebo plus letrozole arm ( $p=0.00028$ ).

The clinical benefit rate was 80.1% (95% CI: 75.2%, 85.0%) in the Ribociclib plus letrozole arm and 71.8% (95% CI: 66.2%, 77.5%) in the placebo plus letrozole arm ( $p=0.018$ ) (see Table 10).

A series of pre-specified subgroup PFS analyses was performed (02 January 2017 cut-off) based on prognostic factors and baseline characteristics to investigate the internal consistency of treatment effect. A reduction in the risk of disease progression or death in favour of the ribociclib plus letrozole arm was observed in all individual patient subgroups of age, race, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone-only metastatic disease. This was evident for patients with liver and/or lung disease (HR of 0.561 [95% CI: 0.424, 0.743], median progression-free survival [mPFS] 24.8 months versus 13.4 months respectively for ribociclib and placebo arm, the same for next) or without liver and/or lung disease (HR of 0.597 [95% CI: 0.426, 0.837], mPFS 27.6 months versus 18.2 months).

Updated results (02 January 2017 cut-off) for overall response and clinical benefit rates are displayed in Table 11.

**Table 10 CLEE011A2301 efficacy results (ORR, CBR) based on Investigator assessment (29 January 2016 cut-off)**

Analysis	Ribociclib plus letrozole (%, 95% CI)	Placebo plus letrozole (%, 95% CI)	p-value <sup>c</sup>
<b>Full analysis set</b>	N=334	N=334	
<b>Overall Response Rate<sup>a</sup></b>	40.7 (35.4, 46.0)	27.5 (22.8, 32.3)	0.000155
<b>Clinical Benefit Rate<sup>b</sup></b>	79.6 (75.3, 84.0)	72.8 (68.0, 77.5)	0.018
<b>Patients with measurable disease</b>	<b>N=256</b>	<b>N=245</b>	
<b>Overall Response Rate<sup>a</sup></b>	52.7 (46.6, 58.9)	37.1 (31.1, 43.2)	0.00028
<b>Clinical Benefit Rate<sup>b</sup></b>	80.1 (75.2, 85.0)	71.8 (66.2, 77.5)	0.020

<sup>a</sup>ORR: proportion of patients with complete response + partial response

<sup>b</sup>CBR: proportion of patients with complete response + partial response + (stable disease or non-complete response/Non-progressive disease  $\geq 24$  weeks)

<sup>c</sup> p-values are obtained from one sided Cochran-Mantel-Haenszel chi-square test.

**Table 11 CLEE011A2301 efficacy results (ORR, CBR) based on investigator assessment (02 January 2017 cut-off)**

Analysis	Ribociclib + letrozole (%, 95% CI)	Placebo + letrozole (%, 95% CI)	p-value <sup>c</sup>
<b>Full analysis set</b>	<b>N=334</b>	<b>N=334</b>	
<b>Overall response rate<sup>a</sup></b>	42.5 (37.2, 47.8)	28.7 (23.9, 33.6)	$9.18 \times 10^{-5}$
<b>Clinical benefit rate<sup>b</sup></b>	79.9 (75.6, 84.2)	73.1 (68.3, 77.8)	0.018
<b>Patients with measurable disease</b>	<b>N=257</b>	<b>N=245</b>	
<b>Overall response rate<sup>a</sup></b>	54.5 (48.4, 60.6)	38.8 (32.7, 44.9)	$2.54 \times 10^{-4}$
<b>Clinical benefit rate<sup>b</sup></b>	80.2 (75.3, 85.0)	71.8 (66.2, 77.5)	0.018

<sup>a</sup> ORR: Overall response rate = proportion of patients with complete response + partial response

<sup>b</sup> CBR: Clinical benefit rate = proportion of patients with complete response + partial response (+ stable disease or non-complete response/Non-progressive disease  $\geq 24$  weeks)

<sup>c</sup> p-values are obtained from one-sided Cochran-Mantel-Haenszel chi-square test

### **Study CLEE011E2301 (MONALEESA-7)**

Ribociclib was evaluated in a randomized, double-blind, placebo-controlled study of ribociclib or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of pre and perimenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer.

A total of 672 [ML7-CSR-Section 10.1] patients were randomized to receive either Ribociclib 600 mg plus tamoxifen or NSAI plus goserelin (n= 335) or placebo plus tamoxifen or NSAI plus goserelin (n= 337), stratified according to the presence of liver and/or lung metastases (Yes [n=344 (51.2%)] versus No [n=328 (48.8%)]) prior chemotherapy for advanced disease (Yes [n=120 (17.9%)] versus No [n=552 (82.1%)]) and endocrine combination partner (NSAI and goserelin) [n=493 (73.4%)] versus tamoxifen and goserelin [n=179 (26.6%)]. Demographics and baseline disease characteristics were balanced and comparable between study arms.

Tamoxifen 20 mg or NSAI (letrozole 2.5 mg or anastrazole 1 mg) were given orally once daily on a continuous schedule, goserelin 3.6 mg administered as sub-cutaneous injection on day 1 of each 28 day cycle, with either Ribociclib 600 mg or placebo orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. Patients were not allowed to cross over from placebo to Ribociclib during the study or after disease progression. Patients were not allowed to switch between endocrine combination partners.

Patients enrolled in the study had a median age of 44 (range 25 to 58) and 27.7% of patients were younger than 40 years of age. The majority of patients were Caucasian (57.7%), Asian (29.5%), or Black (2.8%) and nearly all patients (99.0%) had an ECOG performance status of 0 or 1 of these 672 patients, 14.0% had received prior chemotherapy for metastatic disease. Of the 672 patients, 32.6% of patients had received chemotherapy in the adjuvant vs 18.0% in neo-adjuvant setting and 39.6% had received endocrine therapy in the adjuvant vs 0.7% in neo-adjuvant setting prior to study entry. 40.2% of patients had de novo metastatic disease, 23.7% had bone only disease, and 56.7% had visceral disease.

#### **Overall study**

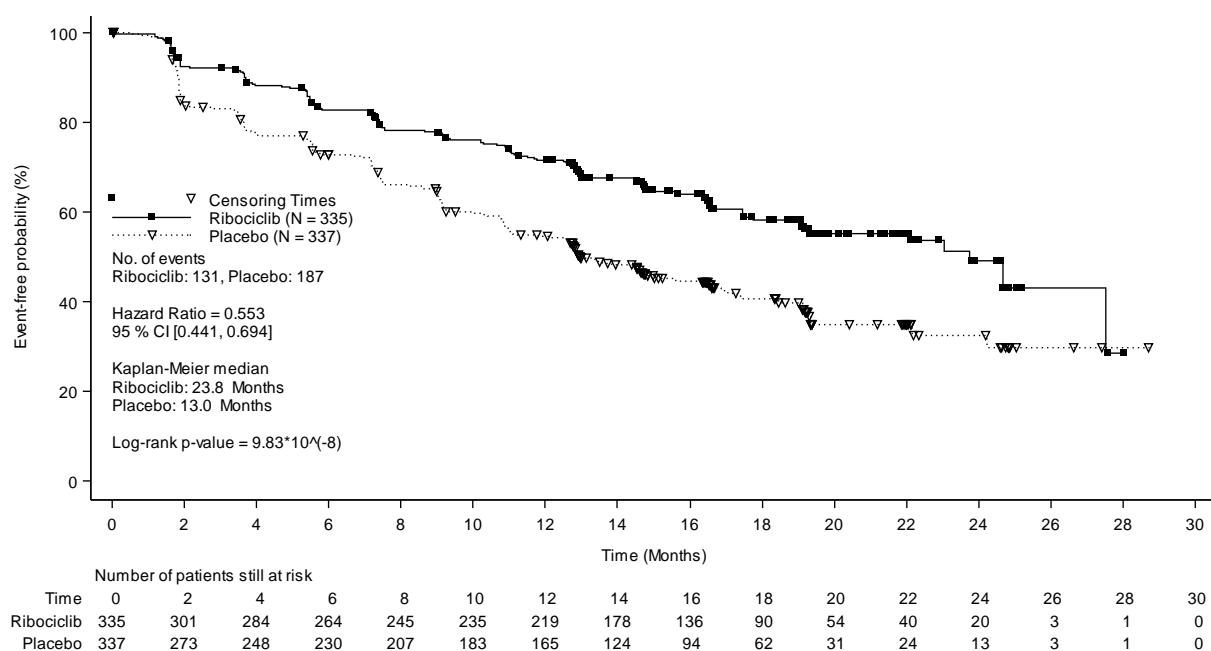
The primary endpoint for the study was performed after observing 318 progression-free survival (PFS) events using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, based on the investigator assessment in the full analysis set (all randomized patients) and confirmed by blinded independent central radiological assessment of a randomly selected subset of approximately 40% of randomized patients. The median follow-up time at the time of primary PFS analysis was 19.2 months.

In the overall study population, the median PFS (95% CI) was 23.8 months (19.2, NE) in the Ribociclib plus tamoxifen or NSAI arm and 13.0 months (11.0, 16.4) in the placebo plus tamoxifen or NSAI arm, [HR: 0.553 (95% CI: 0.441, 0.694), one-sided stratified long-rank test p-value of 9.83x10<sup>-8</sup>]. Efficacy results are summarized in the Kaplan-Meier curve for PFS in Figure 3. At the time of primary PFS analysis, overall survival data were not mature with 89 (35 %) events (N=252, HR 0. 916 [95% CI: 0.601, 1.396]).

The results for PFS based on the blinded independent central radiological assessment of a randomly selected subset of approximately 40% of randomized patients were supportive of the primary efficacy results based on the investigator's assessment (hazard ratio of 0.427; 95% CI: 0.288, 0.633).

Overall response rate (ORR) per Investigator assessment based on RECISTv1.1 was higher in the Ribociclib arm (40.9%; 95% CI: 35.6, 46.2) compared to the placebo arm (29.7%; 95% CI: 24.8, 34.6, p = 0.00098).

The main prespecified QoL measure was Time-To-Deterioration (TTD) in global health status. Definitive 10% deterioration was defined as a worsening in score (EORTC QLQ-C30 global health scale score) by at least 10% compared to baseline, with no later improvement above this threshold observed during the treatment period, or death due to any cause. Addition of Ribociclib to tamoxifen or NSAI resulted in delaying time-to-deterioration in EORTC QLQ-C30 global health scale score compared with placebo plus tamoxifen or NSAI (median not estimable versus 21.2 months; HR of 0.699 [95% CI: 0.533, 0.916]; p=0.004.

**Figure 3****Kaplan-Meier plot of PFS from Monaleesa-7 overall study CLEE011E2301****NSAI sub-group only**

In the pre-specified subgroup analysis of 495 patients who had received Ribociclib or placebo in combination with NSAI plus goserelin, the median PFS (95% CI) was 27.5 months (19.1, NE) in the Ribociclib plus NSAI sub-group and 13.8 months (12.6, 17.4) in the placebo plus NSAI sub-group [HR: 0.569 (95% CI: 0.436, 0.743)]. Efficacy results are summarized in Table 12 and the Kaplan-Meier curves for PFS are provided in Figure 4. Results, in the Ribociclib plus NSAI sub-group were consistent across sub-groups of age, race, prior adjuvant/ neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone only metastatic disease.

In the NSAI subgroup, the median time to response (TTR) was not reached in either the Ribociclib arm or the placebo arm, and the probability of response by 6 months was 34.7% (95% CI: 29.0, 41.1) in the Ribociclib arm and 23.7% (95% CI: 18.8, 29.6) in the placebo arm, indicating that a larger proportion of patients derived earlier benefit in the Ribociclib arm.

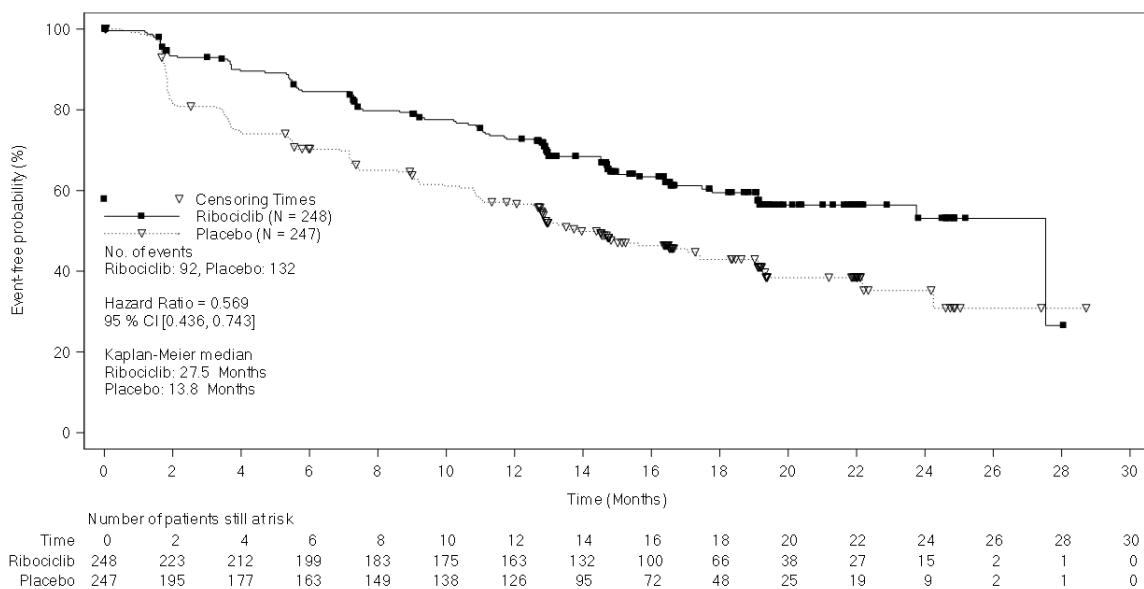
In the NSAI subgroup, the median duration of response (DOR) was not reached (95% CI: 18.3 months, NE) in the Ribociclib arm and was 17.5 months (95% CI: 12.0, NE) in the placebo arm. Among patients with confirmed complete response or partial response, the probability of subsequent progression was 23.5% (95% CI: 15.6, 34.5) in the Ribociclib arm and 36.4% (95% CI: 25.6, 49.8) in the placebo arm at 12 months.

**Table 12** **CLEE011E2301 efficacy results (PFS) from Monaleesa-7 study (E2301) in patients who received NSAI**

	<b>Ribociclib plus NSAI plus goserelin N=248</b>	<b>Placebo plus NSAI plus goserelin N=247</b>
<b>Progression free survival<sup>a</sup></b>		
Median PFS [months] (95% CI)	27.5 (19.1, NE)	13.8 (12.6, 17.4)
Hazard ratio (95% CI)	0.569 (0.436, 0.743)	

*CI=confidence interval; N=number of patients; NE = Not estimable.*

<sup>a</sup> – PFS based on investigator radiological assessment

**Figure 4****Kaplan-Meier plot of PFS based on investigator assessment – Study CLEE011E2301 in patients who received NSAI****Table 13****CLEE011E2301 efficacy results (ORR, CBR) based on investigator assessment in patients who received NSAI**

Analysis	Ribociclib plus NSAI plus goserelin (%, 95% CI)	Placebo plus NSAI plus goserelin (%, 95% CI)
<b>Full analysis set</b>	N=248	N=247
<b>Overall Response Rate<sup>a</sup></b>	39.1 (33.0 , 45.2)	29.1 (23.5 , 34.8)
<b>Clinical Benefit Rate<sup>b</sup></b>	80.2 (75.3, 85.2)	67.2 (61.4 , 73.1)
<b>Patients with measurable disease</b>	<b>N=192</b>	<b>N=199</b>
<b>Overall Response Rate<sup>a</sup></b>	50.5 (43.4 , 57.6)	36.2 (29.5 , 42.9)
<b>Clinical Benefit Rate<sup>b</sup></b>	81.8 (76.3 , 87.2)	63.8 (57.1 , 70.5)

<sup>a</sup>ORR: proportion of patients with complete response + partial response

<sup>b</sup>CBR: proportion of patients with complete response + partial response + (stable disease or non-complete response/Non-progressive disease >=24 weeks)

## NON-CLINICAL SAFETY DATA

Ribociclib was evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity, and phototoxicity studies.

### Safety pharmacology

Ribociclib did not have effects on CNS or respiratory functions. *In vivo* cardiac safety studies in dogs demonstrated dose and concentration related QTc interval prolongation at an exposure that would be expected to

be achieved in patients following the recommended dose of 600 mg. As well, there is potential to induce incidences of PVCs at elevated exposures (approximately 5 fold the anticipated clinical C<sub>max</sub>).

### **Repeated dose toxicity**

Repeated dose toxicity studies (treatment schedule of 3 weeks on/1 week off) in rats up to 26 weeks duration and dogs up to 39 weeks duration, revealed the hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) as the primary target organ of toxicity of ribociclib. Target organs associated with the pharmacological action of ribociclib in repeat dose studies include bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation), kidney (concurrent degeneration and regeneration of tubular epithelial cells) and testes (atrophy). Besides the atrophic changes seen in the testes, which showed a trend towards reversibility, all other changes were fully reversible after a 4-week treatment free period. These effects can be linked to a direct anti-proliferative effect on the testicular germ cells resulting in atrophy of the seminiferous tubules. Exposure to ribociclib in animals in the toxicity studies was generally less than or equal to that observed in patients receiving multiple doses of 600 mg/day (based on AUC).

### **Reproductive toxicity/Fertility**

See section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

### **Genotoxicity**

Genotoxicity studies in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* systems with and without metabolic activation did not reveal any evidence for a mutagenic potential of ribociclib.

### **Phototoxicity**

Ribociclib was shown to absorb light in the UV-B and UV-A range. An *in vitro* phototoxicity test did not identify a relevant phototoxicity potential for ribociclib. The risk that ribociclib causes photosensitization in patients is considered very low.

### **Carcinogenesis**

No carcinogenesis studies have been conducted with ribociclib.

## **INCOMPATIBILITIES**

Not applicable.

## **STORAGE**

See folding box.

KRYXANA should not be used after the date marked "EXPIRY DATE" on the pack.

KRYXANA must be kept out of the sight and reach of children.

## **INSTRUCTIONS FOR USE AND HANDLING**

N/A.

### **Manufacturer:**

See folding box.

### **Importer:**

Sandoz Private Limited, Gala no.11, Building no.27, Arihant Commercial Complex,  
Kopar Bus stop, Purna, Tal- Bhiwandi, Dist- Thane - 421 302, India.

**Marketed By:**

Novartis Healthcare Pvt. Ltd., Gala No. 1-A & 2-A, Bldng No.. 28, Arihant Comp., Kopar, Purna

Tal Bhiwandi-14 (Thane Z5),

Maharashtra, Thane- 421302

(India).

Information issued: India package insert dtd 11 Dec 18 based on the international package leaflet (IPL) dtd 9 Jul 18

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For the use of only Registered Medical Practitioner or a Hospital or a Laboratory

#### Colour code

Oncology

Idiopathic pulmonary fibrosis (IPF)

Both indications

Oncology indication Information highlighted in blue colour and IPF indication information highlighted in purple colour. Information not highlighted in any colour is common for both the indication

## Nintedanib Soft Gelatin Capsules

### CYENDIV®

#### COMPOSITION

#### **CYENDIV® 100 mg**

1 capsule contains 100 mg of nintedanib (= free base) corresponding to 120.4 mg 1*H*-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl)acetyl] amino]phenyl] amino]phenylmethylen]-2-oxo-, methyl ester, (3*Z*)-, ethanesulfonate (1:1) (= nintedanib esilate).

#### **CYENDIV®150 mg**

1 capsule contains 150 mg of nintedanib (= free base) corresponding to 180.6 mg 1*H*-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl)acetyl] amino]phenyl]amino]phenylmethylen]-2-oxo-, methyl ester, (3*Z*)-, ethanesulfonate (1:1) (= nintedanib esilate).

#### **Excipients**

Capsule fill: Medium chain triglycerides, hard fat, lecithin (E322)

Capsule shell: Gelatine, glycerol 85 %, titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), black ink (Opacode®)

Black ink: Shellac glaze, iron oxide black (E172), propylene glycol (E1520)

#### INDICATIONS/ USAGE

**CYENDIV®** is indicated in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first line chemotherapy.

**CYENDIV®** is indicated for the treatment of Idiopathic Pulmonary Fibrosis (IPF)

#### DOSAGE AND ADMINISTRATION/ RECOMMENDED INTAKE

Treatment with **CYENDIV®** should be initiated and supervised by a physician experienced in the use of anticancer therapies.

For posology, method of administration, and dose modifications of docetaxel, please refer to

the corresponding product information for docetaxel.

The recommended dose of **CYENDIV®** is 200 mg twice daily administered approximately 12 hours apart, on days 2 to 21 of a standard 21-day docetaxel treatment cycle.

**CYENDIV®** must not be taken on the same day of docetaxel chemotherapy administration (= day 1).

Treatment with **CYENDIV®** should be initiated by physicians experienced in the diagnosis and treatment of IPF.

The recommended dose of **CYENDIV®** is 150 mg twice daily administered approximately 12 hours apart.

**CYENDIV®** capsules should be taken orally, preferably with food, swallowed whole with water, and should not be chewed or crushed. If a dose is missed, administration should resume at the next scheduled time at the recommended dose. If a dose is missed, the patient should not be given an additional dose.

The recommended maximum daily dose of 400 mg should not be exceeded.

The recommended maximum daily dose of 300 mg should not be exceeded.

Patients may continue therapy with **CYENDIV®** after discontinuation of docetaxel for as long as clinical benefit is observed or until unacceptable toxicity occurs.

### **Dose adjustments**

As initial measure for the management of adverse reactions (see Table 1 and 2) treatment with **CYENDIV®** should be temporarily interrupted until the specific adverse reaction has resolved to levels that allow continuation of therapy (to grade 1 or baseline).

**CYENDIV®** treatment may be resumed at a reduced dose. Dose adjustments in 100 mg steps per day (i.e. a 50 mg reduction per dosing) based on individual safety and tolerability are recommended as described in **Table 1 and Table 2**.

In case of further persistence of the adverse reaction(s), i.e. if a patient does not tolerate 100 mg twice daily, treatment with **CYENDIV®** should be permanently discontinued.

In case of specific elevations of aspartate aminotransferase (AST) / alanine aminotransferase (ALT) values to > 3 x upper limit normal (ULN) in conjunction with an increase of total bilirubin to ≥ 2 x ULN and alkaline phosphatase ALKP < 2 x ULN (see Table 2) treatment with **CYENDIV®** should be interrupted. Unless there is an alternative cause established, **CYENDIV®** should be permanently discontinued (see also section 4.4).

Table 1 Recommended dose adjustments for **CYENDIV®** in case of diarrhoea, vomiting and other non-haematological or haematological adverse reactions except liver enzyme elevations (see Table 2)

CTCAE* Adverse reaction	Dose adjustment
Diarrhoea equal to grade 2 for more than 7 consecutive days despite anti-diarrhoeal treatment**	The geometric mean exposure to nintedanib was 33 % higher in Chinese, Taiwanese, and Indian patients.
<b>OR</b>	

Diarrhoea $\geq$ grade 3 despite anti-diarrhoeal treatment**	<b>The dose reduction was required in 31% Indian patients as observed in the Phase-III NSCLC study</b>
Vomiting ** $\geq$ grade 2 <b>AND/OR</b> Nausea $\geq$ grade 3 despite anti-emetic treatment**	
Other non-haematological or haematological adverse reaction of $\geq$ grade 3	After treatment interruption and recovery to grade 1 or baseline, dose reduction from 200 mg twice daily to 150 mg twice daily and – if a 2 <sup>nd</sup> dose reduction is considered necessary - from 150 mg twice daily to 100 mg twice daily.

\*CTCAE: Common Terminology Criteria for Adverse Events

\*\* see also section *Special warnings and precautions*

Table 2 Recommended dose adjustments for **CYENDIV®** (nintedanib) in case of AST and/or ALT and bilirubin elevations

AST / ALT and bilirubin elevations	Dose adjustment
Elevation of AST and/or ALT values to $> 2.5 \times$ ULN in conjunction with total bilirubin elevation to $\geq 1.5 \times$ ULN <b>OR</b> Elevation of AST and/or ALT values to $> 5 \times$ ULN	After treatment interruption and recovery of transaminase-values to $\leq 2.5 \times$ ULN in conjunction with bilirubin to normal, dose reduction from 200 mg twice daily to 150 mg twice daily and - if a 2nd dose reduction is considered necessary - from 150 mg twice daily to 100 mg twice daily.
Elevation of AST and/or ALT values to $> 3 \times$ ULN in conjunction with an increase of total bilirubin to $\geq 2 \times$ ULN and ALKP $< 2 \times$ ULN	Unless there is an alternative cause established, <b>CYENDIV®</b> should be permanently discontinued.

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase;

ALKP: Alkaline phosphatase; ULN: Upper limit normal

In addition to symptomatic treatment if applicable, the management of side effects (see section *Special warnings and Precautions, Side effects*) of **CYENDIV®** could include dose reduction and temporary interruption until the specific adverse reaction has resolved to levels that allow continuation of therapy. **CYENDIV®** treatment may be resumed at the full dose (150 mg twice daily) or a reduced dose (100 mg twice daily). If a patient does not tolerate 100 mg twice daily, treatment with **CYENDIV®** should be discontinued.

In case of interruptions due to transaminase (AST or ALT) elevations  $> 3 \times$  upper limit of normal (ULN), once transaminases have returned to baseline values, treatment with **CYENDIV®** may be reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full dose (150 mg twice daily). (see section *Special Warnings and Precautions, Side effects*)

### **Special populations**

#### **Paediatric population**

The safety and efficacy of **CYENDIV®** in paediatric patients have not been studied in clinical trials.

### Elderly patients ( $\geq 65$ years)

No overall differences in safety and efficacy were observed for elderly patients compared to patients aged below 65 years. No adjustment of the initial dosing is required on the basis of a patient's age (see section **Pharmacokinetics**).

### Race

Based on population pharmacokinetic (PK) analyses, no *a priori* dose adjustments of CYENDIV® are necessary (see section **Special warnings and precautions**, special populations, **Pharmacokinetics**). Safety data for Black patients are limited.

### Body weight

Based on population PK analyses, no *a priori* dose adjustments of CYENDIV® are necessary (see section Pharmacokinetics).

### Renal impairment

Less than 1 % of a single dose of nintedanib is excreted via the kidney (see section **Pharmacokinetics**). Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 ml/min CrCL).

### Hepatic Impairment

Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90 %; Exposure increased in patients with hepatic impairment (Child Pugh A, Child Pugh B; see section Pharmacokinetics).

No adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child Pugh A, see section Special warnings and precautions).

In patients with mild hepatic impairment (Child Pugh A), the recommended dose of Cyendiv® is 100 mg twice daily approximately 12 hours apart.

In patients with mild hepatic impairment (Child Pugh A), treatment interruption or discontinuation for management of adverse reactions should be considered.

The safety and efficacy of nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B and C. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Cyendiv® is not recommended  
*see section Pharmacokinetics*

## **CONTRAINDICATIONS**

CYENDIV® is contraindicated in patients with known hypersensitivity to nintedanib, peanut or soya, or to any of the excipients .

CYENDIV® is contraindicated during pregnancy (see sections **Fertility, Pregnancy and Lactation** and **Toxicology**).

For contraindications of docetaxel please refer to the corresponding product information for docetaxel.

## **SPECIAL WARNINGS AND PRECAUTIONS**

### Gastrointestinal -Disorders

- *Diarrhoea*  
Diarrhoea was the most frequently reported gastro-intestinal event and appeared in close temporal relationship with the administration of docetaxel (see section ***Side effects***). In the clinical trial LUME-Lung 1 (see section ***Clinical trials***), the majority of patients had mild to moderate diarrhoea. 6.3 % of the patients had diarrhoea of grade  $\geq 3$  in combination treatment compared to 3.6 % treated with docetaxel alone. Diarrhoea should be treated at first signs with adequate hydration and anti-diarrhoeal medicinal products, e.g. loperamide, and may require interruption, dose reduction or discontinuation of therapy with **CYENDIV®** (see section ***Dosage and administration/ Recommended intake***).
- *Nausea and vomiting*  
Nausea and vomiting, mostly of mild to moderate severity, were frequently reported gastrointestinal adverse events (see section ***Side effects***). If symptoms persist despite appropriate supportive care (including anti-emetic therapy), dose reduction, treatment interruption or discontinuation of therapy with **CYENDIV®** (see section ***Dosage and administration/ Recommended intake***) may be required.

Diarrhoea and vomiting may lead to dehydration with or without electrolyte disturbances which may progress to renal function impairment . In the event of dehydration, administration of electrolytes and fluids is required. Plasma levels of electrolytes should be monitored, if relevant gastrointestinal adverse events occur.

#### *Diarrhoea*

In the INPULSIS trials (see section Clinical trials), diarrhoea was the most frequent gastro-intestinal event reported in 62.4 % versus 18.4 % of patients treated with **CYENDIV®** and placebo, respectively (see section ***Side effects***). In most patients the event was of mild to moderate intensity and occurred within the first 3 months of treatment. Diarrhoea led to dose reduction in 10.7% of the patients and to discontinuation of nintedanib in 4.4% of the patients

Diarrhoea should be treated at first signs with adequate hydration and anti-diarrhoeal medicinal products, e.g. loperamide, and may require treatment interruption. **CYENDIV®** treatment may be resumed at a reduced dose (100 mg twice daily) or at the full dose (150 mg twice daily). In case of persisting severe diarrhoea despite symptomatic treatment, therapy with **CYENDIV®** should be discontinued.

- *Nausea and vomiting*  
Nausea and vomiting were frequently reported adverse events (see section ***Side effects***). In most patients with nausea and vomiting, the event was of mild to moderate intensity. Nausea led to discontinuation of nintedanib in 2.0% of patients. Vomiting led to discontinuation in 0.8% of the patients.

If symptoms persist despite appropriate supportive care (including anti-emetic therapy), dose reduction or treatment interruption may be required. The treatment may be resumed at a reduced dose (100 mg twice daily) or at the full dose (150 mg twice daily). In case of persisting severe symptoms therapy with **CYENDIV®** -should

be discontinued.

Diarrhoea and vomiting may lead to dehydration with or without electrolyte disturbances which may progress to renal function impairment.

### Neutropenia and Sepsis

A higher frequency of neutropenia of CTCAE grade > 3 was observed in patients treated with **CYENDIV®** in combination with docetaxel as compared to treatment with docetaxel alone. Subsequent complications such as sepsis or febrile neutropenia have been observed.

Blood counts should be monitored during therapy, in particular during the combination treatment with docetaxel. Frequent monitoring of complete blood counts should be performed at the beginning of each treatment cycle and around the nadir for patients receiving treatment with nintedanib in combination with docetaxel, and as clinically indicated after the administration of the last combination cycle.

### Hepatic Function

The safety and efficacy of **CYENDIV®** has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore treatment with **CYENDIV®** is not recommended in such patients.

Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A; see sections **Dosage and Administration**, **Pharmacokinetics**).

Cases of drug-induced liver injury have been observed with nintedanib treatment. In the post-marketing period, severe liver injury with fatal outcome has been reported. Elevations of liver enzymes (ALT, AST, ALKP, gamma-glutamyltransferase (GGT) and bilirubin were reversible upon dose reduction or interruption in the majority of cases.

Transaminase, ALKP and bilirubin levels should be investigated upon initiation of the combination treatment with **CYENDIV®** plus docetaxel. The values should be monitored as clinically indicated or periodically during treatment, i.e. in the combination phase with docetaxel at the beginning of each treatment cycle and monthly in case **CYENDIV®** is continued as monotherapy after discontinuation of docetaxel.

If relevant liver enzyme elevations are measured, interruption, dose reduction or discontinuation of the therapy with **CYENDIV®** may be required (see section **Dosage and administration/Table 2**). Alternative causes of the liver enzyme elevations should be investigated and respective action should be taken as necessary.

In case of specific changes in liver values (AST/ALT > 3 x ULN in conjunction with bilirubin  $\geq$  2 x ULN and ALKP < 2 x ULN) treatment with **CYENDIV®** should be interrupted. Unless there is an alternative cause established, **CYENDIV®** should be permanently discontinued (see section **Dosage and administration/Table 2**).

Female and Asian patients have a higher risk of elevations in liver enzymes. Nintedanib exposure increased linearly with patient age and was inversely correlated to weight which may also result in a higher risk of developing liver enzyme elevations (see

section Pharmacokinetics).

Close monitoring is recommended in patients with these risk factors.

Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A). Patients with mild hepatic impairment (Child Pugh A) should be treated with a reduced dose of CYENDIV® (see sections Dosage and Administration, Pharmacokinetics)

Cases of drug-induced liver injury have been observed with nintedanib treatment. In the post-marketing period, non-serious and serious cases of drug-induced liver injury, including severe liver injury with fatal outcome, have been reported.

The majority of hepatic events occur within the first three months of treatment. Therefore, hepatic transaminase and bilirubin levels should be investigated upon initiation of treatment with CYENDIV®, at regular intervals during the first three months of treatment and periodically thereafter (e.g. at each patient visit) or as clinically indicated.

Elevations of liver enzymes (ALT, AST, ALKP, gamma-glutamyl-transferase (GGT)) and bilirubin were reversible upon dose reduction or interruption in the majority of cases. If transaminase (AST or ALT) elevations > 3x upper limit of normal (ULN) are measured, dose reduction or interruption of the therapy with CYENDIV® is recommended and the patient should be monitored closely. Once transaminases have returned to baseline values, treatment with CYENDIV® may be re-increased to the full dose (150 mg twice daily) or reintroduced at a reduced dose (100 mg twice daily) which subsequently may be increased to the full dose. (see section **Dosage and administration/Recommended intake**). If any liver test elevations are associated with clinical signs or symptoms of liver injury, e.g. jaundice, treatment with CYENDIV® should be permanently discontinued. Alternative causes of the liver enzyme elevations should be investigated.

Patients with low body weight (< 65 kg), Asian and female patients have a higher risk of elevations in liver enzymes.

Nintedanib exposure increased linearly with patient age, which may also result in a higher risk of developing liver enzyme elevations (see section Pharmacokinetics).

Close monitoring is recommended in patients with these risk factors

### Haemorrhage

VEGFR inhibition might be associated with an increased risk of bleeding. In the clinical trial (LUME-Lung 1) with CYENDIV®, the frequency of bleeding in both treatment arms was comparable. Mild to moderate epistaxis represented the most frequent bleeding event. There were no imbalances of respiratory or fatal bleedings and no intracerebral bleeding was reported. The majority of fatal bleeding events were tumour associated.

In the post-marketing period non-serious and serious bleeding events, some of which were fatal, have been observed. In patients who experience grade 3/4 bleeding events, the benefits and risks of continuing treatment with CYENDIV® should be carefully weighed and discontinuation of CYENDIV® may be considered. If treatment with CYENDIV® is resumed, a reduced daily dose is recommended (see section **Dosage and administration/Table 1**).

Patients with recent pulmonary bleeding (> 2.5 ml of red blood) as well as patients with centrally located tumours with radiographic evidence of local invasion of major blood vessels or radiographic evidence of cavitary or necrotic tumours have been excluded from clinical trials. Therefore, it is not recommended to treat these patients with CYENDIV®.

- Brain metastasis

- *Stable brain metastasis*

No increased frequency of cerebral bleeding in patients with adequately pre-treated brain metastases which were stable for  $\geq 4$  weeks before start of treatment with **CYENDIV®** was observed. However, such patients should be closely monitored for signs and symptoms of cerebral bleeding.

- *Active brain metastasis*

Patients with active brain metastasis were excluded from clinical trials and are not recommended for treatment with **CYENDIV®**.

- Therapeutic anticoagulation

There are no data available for patients with inherited predisposition to bleeding or for patients receiving a full dose of anticoagulative treatment prior to start of treatment with **CYENDIV®**. In patients on chronic low dose therapy with low molecular weight heparins or acetylsalicylic acid, no increased frequency of bleeding was observed. Patients who developed thromboembolic events during treatment and who required anticoagulant treatment were allowed to continue **CYENDIV®** and did not show an increased frequency of bleeding events. Patients taking concomitant anticoagulation, such as warfarin or phenprocoumon should be monitored regularly for changes in prothrombin time, INR, or clinical bleeding episodes.

VEGFR inhibition might be associated with an increased risk of bleeding. In the INPULSIS trials with **CYENDIV®**, the frequency of patients who experienced bleeding adverse events was slightly higher in the **CYENDIV®** arm (10.3%) than in the placebo arm (7.8%). Non-serious epistaxis was the most frequent bleeding event. Serious bleeding events occurred with low and similar frequencies in the 2 treatment groups (placebo: 1.4%; Cyendiv: 1.3%). Patients at known risk for bleeding including patients with inherited predisposition to bleeding or patients receiving a full dose of anticoagulative treatment were not included in the INPULSIS studies. Therefore these patients should only be treated with **CYENDIV®** if the anticipated benefit outweighs the potential risk. In the post-marketing period non-serious and serious bleeding events, some of which were fatal, have been observed.

### Arterial thromboembolic events

The frequency of arterial thromboembolic events was comparable between the two treatment arms in the phase 3 study 1199.13 (LUME-Lung 1). Patients with a recent history of myocardial infarction or stroke were excluded from this study. However, an increased frequency of arterial thromboembolic events was observed in patients with idiopathic pulmonary fibrosis (IPF) when treated with nintedanib monotherapy.

Patients with a recent history of myocardial infarction or stroke were excluded from the INPULSIS trials. Arterial thromboembolic events were infrequently reported: in 0.7% of patients in the placebo and 2.5% in the nintedanib treated group.

While adverse events reflecting ischaemic heart disease were balanced between the nintedanib and placebo groups, a higher percentage of patients experienced myocardial infarctions in the nintedanib group (1.6%) compared to the placebo group (0.5%).

Use caution when treating patients with a higher cardiovascular risk including known coronary artery disease. Treatment interruption should be considered in patients who develop signs or symptoms of acute myocardial ischaemia.

## Venous thromboembolism

Patients treated with **CYENDIV®** have an increased risk of venous thromboembolism including deep vein thrombosis. Patients should be closely monitored for thromboembolic events. **CYENDIV®** should be discontinued in patients with life-threatening venous thromboembolic reactions.

In the INPULSIS trials no increased risk of venous thromboembolism was observed in nintedanib treated patients. Due to the mechanism of action of nintedanib patients might have an increased risk of thromboembolic events.

## Gastrointestinal perforations

The frequency of gastrointestinal perforation was comparable between the treatment arms in the LUME-Lung 1 study. **Due to the mechanism of action nintedanib patients might have an increased risk of gastrointestinal perforations.** Cases of gastrointestinal perforations, some of which were fatal, have been reported in the post-marketing period. Particular caution should be exercised when treating patients with previous abdominal surgery or a recent history of a hollow organ perforation. **CYENDIV®** should therefore only be initiated at least 4 weeks after major, incl. abdominal, surgery. Therapy with **CYENDIV®** should be permanently discontinued in patients who develop gastrointestinal perforation.

In the INPULSIS trials no increased risk of gastrointestinal perforation was observed in nintedanib treated patients. **Due to the mechanism of action nintedanib patients might have an increased risk of gastrointestinal perforations.** Cases of gastrointestinal perforations, some of which were fatal, have been reported in the post-marketing period. Particular caution should be exercised when treating patients with previous abdominal surgery, or a recent history of a hollow organ perforation, previous history of peptic ulceration, diverticular disease or receiving concomitant corticosteroids or NSAIDs. **CYENDIV®** should therefore only be initiated at least 4 weeks after major, incl. abdominal, surgery. Therapy with **CYENDIV®** should be permanently discontinued in patients who develop gastrointestinal perforation.

## Wound healing complication

Based on the mechanism of action nintedanib may impair wound healing. No increased frequency of impaired wound healing was observed in the clinical trials. No dedicated studies investigating the effect of nintedanib on wound healing were performed. Treatment with **CYENDIV®** should therefore only be initiated or - in case of perioperative interruption - resumed based on clinical judgement of adequate wound healing.

## Soya lecithin

**CYENDIV®** contains soya lecithin. If you are allergic to peanut or soya, do not use this medicinal product.

## Special populations

In study 1199.13 (LUME-Lung 1), there was a higher frequency of serious adverse events in patients treated with nintedanib plus docetaxel with a body weight of less than 50 kg

compared to patients with a weight  $\geq 50$  kg; however the number of patients with a body weight of less than 50 kg was small. Therefore close monitoring is recommended in patients weighing  $< 50$  kg.

## **INTERACTIONS**

### P-glycoprotein (P-gp)

Nintedanib is a substrate of P-gp (see section ***Pharmacokinetics***). Co-administration with the potent P-gp inhibitor ketoconazole increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on  $C_{max}$  in a dedicated drug-drug interaction study.

In a drug-drug interaction study with the potent P-gp inducer rifampicin, exposure to nintedanib decreased to 50.3 % based on AUC and to 60.3 % based on  $C_{max}$  upon co-administration with rifampicin compared to administration of nintedanib alone.

If co-administered with **CYENDIV®**, potent P-gp inhibitors (e.g. ketoconazole or erythromycin) may increase exposure to nintedanib. In such cases, patients should be monitored closely for tolerability of nintedanib. Management of side effects may require interruption, dose reduction, or discontinuation of therapy with **CYENDIV®** (see section ***Dosing and administration***).

Potent P-gp inducers (e.g. rifampicin, carbamazepine, phenytoin, and St. John's Wort) may decrease exposure to nintedanib. Selection of an alternate concomitant medication with no or minimal P-gp induction potential should be considered.

### Food

**CYENDIV®** is recommended to be taken with food (see section ***Pharmacokinetics***).

### Cytochrome (CYP)-enzymes

Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways. Nintedanib and its metabolites, the free acid moiety BIBF 1202 and its glucuronide BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes in preclinical studies (see section ***Pharmacokinetics***). The likelihood of drug-drug interactions with nintedanib based on CYP metabolism is therefore considered to be low.

### Co-administration with other drugs

Co-administration of nintedanib with docetaxel ( $75$  mg/m $^2$ ) did not alter the pharmacokinetics of either drug to a relevant extent.

The potential for interactions of nintedanib with hormonal contraceptives was not explored.

## **FERTILITY, PREGNANCY AND LACTATION**

### Fertility

Based on preclinical investigations, there is no evidence for impairment of male fertility (see section ***Toxicology***). From subchronic and chronic toxicity studies, there is no evidence that female fertility in rats is impaired at a systemic exposure level comparable with that at the maximum recommended human dose (MRHD) of 200 mg twice daily (see section ***Toxicology***).

Based on preclinical investigations, there is no evidence for impairment of male fertility (see section **Toxicology**). From subchronic and chronic toxicity studies, there is no evidence that female fertility in rats is impaired at a systemic exposure level comparable with that at the maximum recommended human dose (MRHD) of 150 mg twice daily (see section **Toxicology**).

### Contraception

Women of childbearing potential being treated with **CYENDIV®** should be advised to use adequate contraception during and at least 3 months after the last dose of **CYENDIV®**. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with **CYENDIV®**.

### Pregnancy

There is no information on the use of **CYENDIV®** in pregnant women, but pre-clinical studies in animals have shown reproductive toxicity of this drug (see section **Toxicology** ). As nintedanib may cause foetal harm also in humans, it must not be recommended during pregnancy and pregnancy testing should be conducted at least prior to treatment with **CYENDIV®**.

Female patients should be advised to notify their doctor or pharmacist if becoming pregnant during therapy with **CYENDIV®**.

If the patient becomes pregnant while receiving **CYENDIV®** the patient should be apprised of the potential hazard to the foetus. Termination of the treatment should be considered.

### Breastfeeding / lactation

There is no information on the excretion of nintedanib and its metabolites in human milk. Pre-clinical studies showed that small amounts of nintedanib and its metabolites ( $\leq 0.5\%$  of the administered dose) were secreted into milk of lactating rats.

A risk to the newborns/infants cannot be excluded. Breastfeeding should be discontinued during treatment with **CYENDIV®**.

For fertility, pregnancy and lactation information for docetaxel please refer to the corresponding product information for docetaxel.

## **EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

No studies of the effects on the ability to drive and use machines have been performed. Patients should be advised to be cautious when driving or using machines during treatment with **CYENDIV®**.

### **SIDE EFFECTS**

#### Summary of the safety profile

The safety data provided in the following are based on the global, double-blind randomised pivotal phase 3 trial 1199.13 (LUME-Lung 1) comparing treatment with nintedanib plus docetaxel against placebo plus docetaxel in patients with locally advanced, or metastatic, or recurrent NSCLC after first-line chemotherapy and based on data observed during the post-marketing period. **The most frequently reported adverse reactions specific for nintedanib were diarrhoea, increased liver enzyme values (ALT and AST) and vomiting. Table 3 provides a summary of the adverse reactions by System Organ Class**

(SOC).

Nintedanib has been studied in clinical trials of 1529 patients suffering from Idiopathic Pulmonary Fibrosis (IPF).

The safety data provided in the following are based on the two Phase 3, randomised, double-blind, placebo-controlled studies in 1061 patients comparing treatment with nintedanib 150 mg twice daily to placebo for 52 weeks (INPULSIS-1 and INPULSIS-2) and based on data observed during the post-marketing period.

The most frequently reported adverse events associated with the use of nintedanib included diarrhoea, nausea and vomiting, abdominal pain, decreased appetite, weight decreased and hepatic enzyme increased.

For the management of selected adverse reactions please also refer to section ***Special Warnings and Precautions.***

Table 3 Summary of Adverse Reactions in trial LUME- Lung 1  
(NSCLC patients of adenocarcinoma histology)

<b>System Organ Class - MedDRA terminology –</b>	<b>CCDS verbatim term MedDRA (version 15.1) PTs</b>	<b>Frequency category according to EU SmPC Guideline</b>
Infections and infestations	Sepsis	Common
	Abscess	Common
	Febrile neutropenia	Common
Blood and lymphatic system	Neutropenia**	Very common
	Thrombocytopenia	Common
Metabolism and nutrition	Dehydration	Common
	Electrolyte imbalance	Very common
	Decreased appetite	Very common
	Weight decreased	Common
Vascular disorders	Hypertension	Common
	Venous thromboembolism	Common
	Bleeding	Very common
Gastrointestinal Disorder	Diarrhea	Very common
	Vomiting	Very common
	Abdominal pain	Very common
	Perforation	Uncommon
	Nausea	Very common
	Stomatitis	Very common
	Pancreatitis	Uncommon
Hepatobiliary disorders	Drug-induced liver injury	Uncommon
	Alanine aminotransferase increased	Very common
	Aspartate aminotransferase increased	Very common
	Blood alkaline Phosphatase increased	Very common
	Gamma-Glutamyltransferse increased	Common
	Hyperbilirubinemia	Common
Skin and subcutaneous tissue	Mucositis***	Very common
	Rash	Very common
	Pruritus	Common
Nervous system disorders	Peripheral neuropathy	Very common

- 1) Please also refer to the product information for docetaxel.
- 2) Frequency was not increased in patients treated with nintedanib plus docetaxel as compared to placebo plus docetaxel.
- 3) Events of pancreatitis have been reported in patients taking nintedanib for the treatment of IPF and NSCLC. The majority of these events were reported for patients in the IPF indication.

Table 4 Summary of Adverse Reactions in randomised Phase III trials (IPF)

<b>System Organ Class - MedDRA terminology –</b>	<b>CCDS verbatim term MedDRA (version 16.1) PTs</b>	<b>Frequency category according to EU SmPC Guideline</b>
Blood and lymphatic system	Thrombocytopenia	Uncommon
Metabolism and nutrition disorders	Decreased appetite	Common
	Weight decreased	Common
Vascular disorders	Hypertension	Uncommon
	Bleeding <sup>1</sup>	Common
Gastrointestinal disorders	Diarrhoea	Very common
	Nausea	Very common
	Abdominal pain	Very common
	Vomiting	Common
	Pancreatitis	Uncommon
Hepatobiliary disorders	Drug-induced liver injury	Uncommon
	Hepatic enzyme increased	Very common
	Alanine aminotransferase increased	Common
	Aspartate aminotransferase increased	Common
	Gamma-glutamyltransferase increased	Common
	Blood alkaline Phosphatase increased	Uncommon
	Hyperbilirubinaemia	Uncommon
Skin and subcutaneous tissue	Rash	Common
	Pruritus	Uncommon

<sup>1</sup> Exceptionally LLT

1) Term represents a group of events that describe a broader medical concept rather than a single condition or MedDRA preferred term.

2) Non-serious and serious bleeding events , some of which were fatal have been observed in the post-marketing period in line with clinical trial experience

## **SAFETY MONITORING**

**Reporting all serious adverse reactions after approval of the Nintedanib capsules is important. It allows continued monitoring of the benefit/risk balance of the product. Indian patients being treated with this drug should be monitored closely for any untoward occurrence and overall safety of the patients.**

**Healthcare professionals are requested to monitor and report all serious adverse reactions and report the same to Pharmacovigilance Programme of India (PvPI) Email**

## **OVERDOSE**

There is no specific antidote or treatment for **CYENDIV®** overdose. The highest single dose of nintedanib administered in phase I studies was 450 mg once daily. In addition, 2 patients in the oncology programme had an overdose of maximum 600 mg twice daily (b.i.d) up to eight days. Observed adverse events were consistent with the known safety profile of nintedanib, i.e. increased liver enzymes and gastrointestinal symptoms. Both patients recovered from these adverse reactions.

In the INPULSIS trials, one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (*nasopharyngitis*) occurred and resolved during the period of incorrect dosing, with no onset of other reported events.

In case of overdose, treatment should be interrupted and general supportive measures initiated as appropriate.

## **PHARMACOLOGICAL PROPERTIES**

Pharmacotherapeutic group: Antineoplastic agents - Protein-tyrosine kinase inhibitors.  
ATC code: L01XE31

### Mechanism of action

Nintedanib is a triple angiokinase inhibitor blocking vascular endothelial growth factor receptors (VEGFR 1-3), platelet-derived growth factor receptors (PDGFR  $\alpha$  and  $\beta$ ) and fibroblast growth factor receptors (FGFR 1-3) kinase activity. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signalling which is crucial for the proliferation and survival of endothelial as well as perivascular cells (pericytes and vascular smooth muscle cells). In addition Fms-like tyrosine-protein kinase (Flt)-3, lymphocyte-specific tyrosine-protein kinase (Lck) and proto-oncogene tyrosine-protein kinase Src (Src) are inhibited.

Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet-derived growth factor receptor (PDGFR)  $\alpha$  and  $\beta$ , fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3. Nintedanib binds competitively to the ATP binding pocket of these receptors and blocks the intracellular signalling which is crucial for the proliferation, migration and transformation of fibroblasts representing essential mechanisms of the IPF pathology. In addition nintedanib inhibits Flt-3, Lck, Lyn and Src kinases.

### Pharmacodynamic effects

Tumour angiogenesis is an essential feature contributing to tumour growth, progression and metastasis formation and is predominantly triggered by the release of pro-angiogenic factors secreted by the tumour cell (i.e. VEGF and bFGF) to attract host endothelial as well as perivascular cells to facilitate oxygen and nutrient supply through the host vascular system. In preclinical disease models nintedanib, as single agent, effectively interfered with the formation and maintenance of the tumour vascular system resulting in tumour growth inhibition and tumour stasis. In particular, treatment of tumour xenografts with nintedanib

led to a rapid reduction in tumour micro vessel density, pericytes vessel coverage and tumour perfusion.

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) measurements showed an anti-angiogenic effect of nintedanib in humans. It was not clearly dose dependent, but most responses were seen at doses of  $\geq$  200 mg. Logistic regression revealed a statistically significant association of the anti-angiogenic effect to nintedanib exposure. DCE-MRI effects were seen 24-48 h after the first intake of the medicinal product and were preserved or even increased after continuous treatment over several weeks. No correlation of the DCE-MRI response and subsequent clinically significant reduction in target lesion size was found, but DCE-MRI response was associated with disease stabilization.

Activation of FGFR and PDGFR signalling cascades is critically involved in proliferation and migration of lung fibroblasts/myofibroblasts, the hallmark cells in the pathology of idiopathic pulmonary fibrosis . The potential impact of VEGFR inhibition on IPF pathology is currently not fully elucidated. On the molecular level, nintedanib is thought to inhibit the FGFR and PDGFR signalling cascades mediating lung fibroblast proliferation and migration by binding to the adenosine triphosphate (ATP) binding pocket of the intracellular receptor kinase domain, thus interfering with cross-activation via auto-phosphorylation of the receptor homodimers. In vitro, the target receptors are inhibited by nintedanib in low nanomolar concentrations. In human lung fibroblasts from patients with IPF nintedanib inhibited PDGF-, FGF-, and VEGF-stimulated cell proliferation with EC<sub>50</sub> values of 11 nmol/L, 5.5 nmol/L and less than 1 nmol/L, respectively. At concentrations between 100 and 1000 nmol/L nintedanib also inhibited PDGF-, FGF-, and VEGF-stimulated fibroblast migration and TGF- $\beta$ 2-induced fibroblasts to myofibroblast transformation. In addition, the anti-inflammatory activity of nintedanib is thought to limit fibrotic stimulation by reduction of profibrotic mediators like IL-1 $\beta$  and IL-6. The contribution of the anti-angiogenic activity of nintedanib to its mechanism of action in fibrotic lung diseases is currently not clarified. In in vivo studies, nintedanib was shown to have potent anti-fibrotic and anti-inflammatory activity.

## **CLINICAL TRIALS**

### **Efficacy in the pivotal phase 3 trial LUME-Lung 1**

The efficacy and safety of Nintedanib was investigated in 1314 patients with locally advanced, metastatic or recurrent NSCLC after one prior line of chemotherapy. The trial included 658 patients (50.1 %) with adenocarcinoma, 555 patients (42.2 %) with squamous cell carcinoma, and 101 patients (7.7 %) with other tumour histologies.

Patients were randomized (1:1) to receive nintedanib 200 mg orally twice daily in combination with 75 mg/m<sup>2</sup> of i.v. docetaxel every 21 days (n = 655) or placebo orally twice daily in combination with 75 mg/m<sup>2</sup> of docetaxel every 21 days (n = 659). Randomization was stratified according to Eastern Cooperative Oncology Group (ECOG) status (0 vs. 1), bevacizumab pretreatment (yes vs. no), brain metastasis (yes vs. no) and tumour histology (squamous vs. non-squamous tumour histology).

Patient characteristics were balanced between treatment arms within the overall population and within the adenocarcinoma patients. In the overall population 72.7 % of the patients were male. The majority of patients were non-Asian (81.6 %), the median age was 60.0 years, the baseline ECOG performance status was 0 (28.6 %) or 1 (71.3 %); one patient had a baseline ECOG performance status of 2. 5.8 % of the patients had stable brain metastasis at study entry and 3.8 % had prior bevacizumab treatment.

The disease stage was determined at the time of diagnosis using Union Internationale Contre le Cancer (UICC) / American Joint Committee on Cancer (AJCC) Edition 6 or Edition 7. In the overall population, 16.0 % of the patients had disease stage < IIIB/IV, 22.4 %, had disease stage IIIB and 61.6 % had disease stage IV. 9.2 % of the patients entered the study with locally recurrent disease stage as had been evaluated at baseline. For patients with tumour of adenocarcinoma histology, 15.8 % had disease stage < IIIB/IV, 15.2 %, had disease stage IIIB and 69.0 % had disease stage IV.

5.8 % of the adenocarcinoma patients entered the study with locally recurrent disease stage as had been evaluated at baseline. 'Locally recurrent' was defined as local re-occurrence of the tumour without metastases at study entry.

The primary endpoint was progression-free survival (PFS) as assessed by an independent review committee (IRC) based on the intent-to-treat (ITT) population and tested by histology. Overall survival (OS) was the key secondary endpoint. Other efficacy outcomes included objective response, disease control, change in tumour size and health-related quality of life.

As shown in **Table 5**, the addition of nintedanib to docetaxel led to a statistically significant reduction in the risk of progression or death by 21 % for the overall population (HR 0.79; 95 % CI: 0.68 - 0.92; p = 0.0019) as determined by the IRC. This result was confirmed in the follow-up PFS analysis (HR 0.85, 95 % CI: 0.75 - 0.96; p = 0.0070) which included all events collected at the time of the final OS analysis. Overall survival analysis in the overall population did not reach statistical significance (HR 0.94; 95% CI: 0.83 - 1.05).

Of note, pre-planned analyses according to histology showed statistically significant difference in OS between treatment arms in the adenocarcinoma population only.

The addition of nintedanib to docetaxel led to a statistically significant reduction in the risk of progression or death by 23 % for the adenocarcinoma population (HR 0.77; 95% CI: 0.62 - 0.96). In line with these observations, related study endpoints such as disease control and change in tumour size showed significant improvements.

Table 5 Efficacy results for study LUME-Lung 1 for all patients and for patients with adenocarcinoma tumour histology

	All patients		Adenocarcinoma tumour histology	
	Nintedanib b (n = 565)	Placebo (n = 569)	Nintedanib (n = 277)	Placebo (n = 285)
<b>Progression free survival*</b>				
Number of Deaths or Progressions, n (%)	339 (60.0)	375 (65.9)	152 (54.9)	180 (63.2)
Median PFS [months]	3.4	2.7	4.0	2.8
HR (95% CI)**	0.79 (0.68, 0.92)		0.77 (0.62, 0.96)	
Stratified Log-Rank Test p-value**		0.0019		0.0193
Disease control [%]	48.5	37.6	60.6	43.9
Odds ratio (95% CI) <sup>+</sup>	1.56 (1.23, 1.98)		1.98 (1.41, 2.77)	
p-value <sup>+</sup>	0.0002		<0.0001	
Objective response [%]	3.4	1.9	4.3	3.5
Odds ratio (95% CI) <sup>+</sup>	1.77 (0.85, 3.89)		1.25 (0.53, 3.01)	
p-value <sup>+</sup>	0.1283		0.6122	
Adjusted mean of best % change of tumour size from baseline [%]	-3.93	1.15	-7.38	-0.28
p-value <sup>o</sup>		0.0002		0.0002
<b>Overall Survival***</b>				
	(n= 655)	(n= 659)	(n= 322)	(n= 336)
Number of OS events, n (%)	564 (86.1)	557 (84.5)	259 (80.4)	276 (82.1)
Median OS [months]	10.1	9.1	12.6	10.3
HR (95% CI)	0.94 (0.83, 1.05)		0.83 (0.70, 0.99)	
Stratified Log-Rank Test p-value*		0.2720		0.0359

\* Primary PFS analysis based on a total of 713<sup>th</sup> PFS events in the overall population.

\*\* Stratified by baseline ECOG PS (0 vs. 1), brain metastases at baseline (yes vs. no) and prior treatment with bevacizumab (yes vs. no).and in the all patients population it is additionally stratified by tumour histology (squamous vs. non-squamous).

\*\*\* OS analysis based on a total of 1121 deaths in the overall population

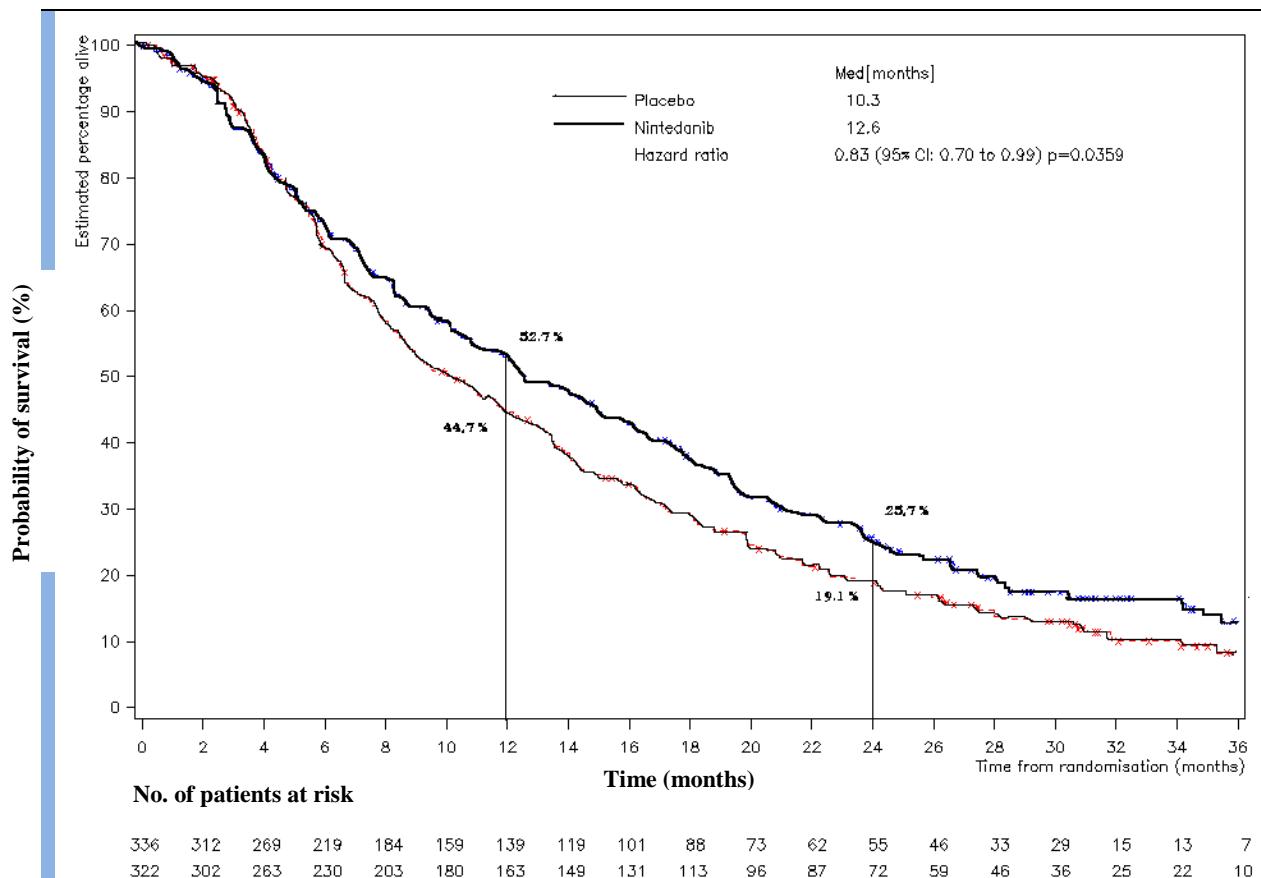
+ Odds ratio and p-value are obtained from a logistic regression model adjusted for baseline ECOG Performance Score (0 vs. 1) and in the all patients population it is additionally adjusted by tumour histology (squamous vs. non-squamous).

o Adjusted mean of best % change from baseline and p-value generated from an ANOVA model adjusting for baseline ECOG PS (0 vs. 1), brain metastases at baseline (yes vs. no) and prior treatment with bevacizumab (yes vs. no). In the all patients population it is additionally adjusted by tumour histology (squamous vs. non-squamous). One patient (135301) has a baseline ECOG PS of 2.

A statistically significant improvement in OS favouring treatment with nintedanib plus docetaxel was demonstrated in patients with adenocarcinoma with a 17 % reduction in the risk of death (HR 0.83, p = 0.0359) and a median OS improvement of 2.3 months (10.3 vs. 12.6 months, **Figure 1**).

Figure 1

Kaplan-Meier Curve for overall survival for patients with adenocarcinoma tumour histology by treatment group in trial LUME-Lung 1



A pre-specified evaluation was performed in the population of adenocarcinoma patients considered to have entered the study with a particularly poor treatment prognosis, namely, patients who progressed during or shortly after 1<sup>st</sup> line therapy prior to study entry. This population included those adenocarcinoma patients identified at baseline as having progressed and entered the study less than 9 months since start of their first-line therapy. Treatment of these patients with nintedanib in combination with docetaxel reduced the risk of death by 25 %, compared with placebo plus docetaxel (HR 0.75; 95 % CI: 0.60 - 0.92; p = 0.0073). Median OS improved by 3 months (nintedanib: 10.9 months; placebo: 7.9 months).

In a post-hoc analysis in adenocarcinoma patients having progressed and entered the study  $\geq$  9 months since start of their first-line therapy the difference did not reach statistical significance (HR for OS: 0.89, 95% CI 0.66 - 1.19).

The proportion of adenocarcinoma patients with stage < IIIB/IV at diagnosis was small and balanced across treatment arms (placebo: 54 patients (16.1 %); nintedanib: 50 patients, (15.5 %)). The HR for these patients for PFS and OS was 1.24 (95% CI: 0.68, 2.28) and 1.09 (95% CI: 0.70, 1.70), respectively. However, the sample size was small, there was no significant interaction and the CI was wide and included the HR for OS of the overall adenocarcinoma population.

The clinical efficacy of nintedanib has been studied in patients with IPF in two phase 3, randomised, double-blind, placebo-controlled studies with identical design (INPULSIS-1 and INPULSIS-2). Patients were randomised in a 3:2 ratio to treatment with Nintedanib Capsules 150 mg or placebo twice daily for 52 weeks.

The primary endpoint was the annual rate of decline in Forced Vital Capacity (FVC). The key secondary endpoints were change from baseline in Saint George's Respiratory Questionnaire (SGRQ) total score at 52 weeks and time to first acute IPF exacerbation.

Annual rate of decline in FVC

The annual rate of decline of FVC (in mL) was significantly reduced in patients receiving nintedanib compared to patients receiving placebo. The treatment effect was consistent in both trials. See Table 6 for individual and pooled study results.

Table 6 Annual rate of decline in FVC (mL) in trials INPULSIS-1, INPULSIS-2 and their pooled data - treated set

INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
Placebo	Nintedanib capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily
Number of patients	204	309	219	329	423
Rate <sup>1</sup> (SE) of decline over 52 weeks	-239.9 (18.71)	-114.7 (15.33)	-207.3 (19.31)	-113.6 (15.73)	-223.5 (13.45) -113.6 (10.98)
Comparison vs placebo Difference <sup>1</sup>		125.3		93.7	109.9
95% CI	(77.7, 172.8)		(44.8, 142.7)		(75.9, 144.0)
p-value	<0.0001		0.0002		<0.0001

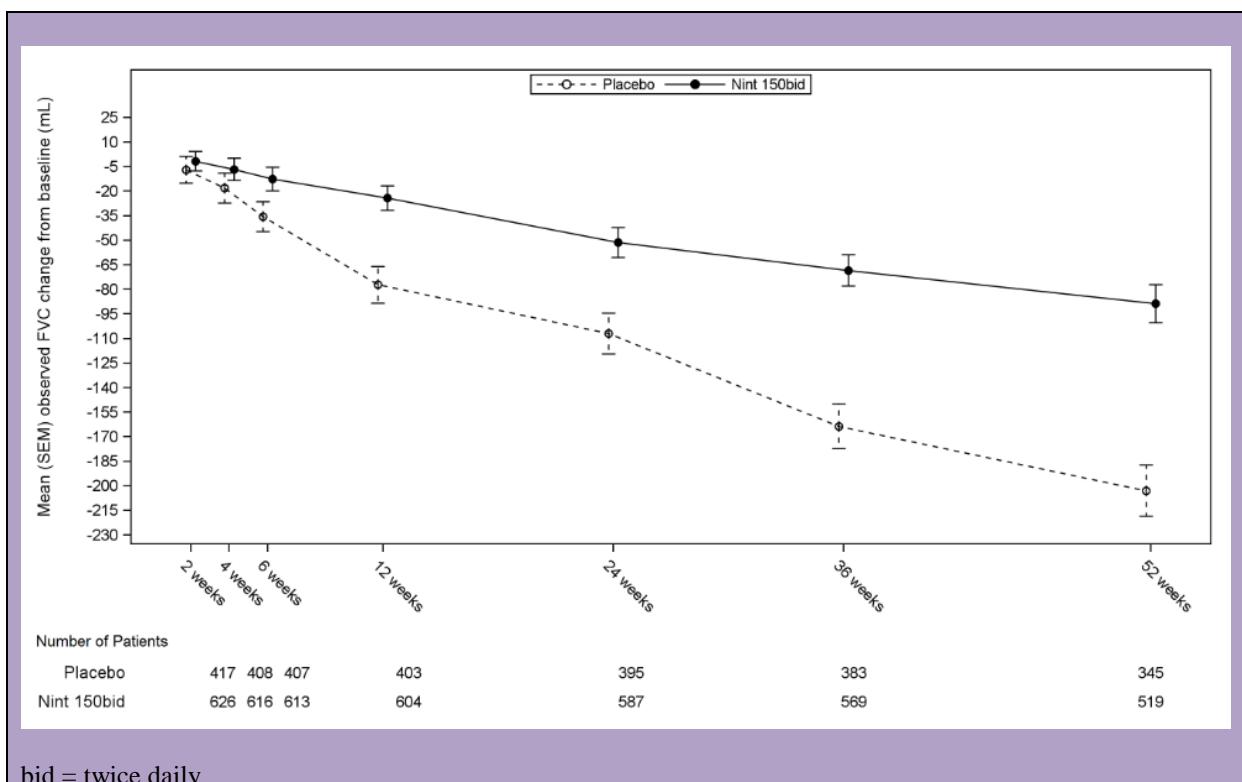
<sup>1</sup> Estimated based on a random coefficient regression model.

The robustness of the effect of nintedanib in reducing the annual rate of decline in FVC was confirmed in all pre-specified sensitivity analyses.

In addition, similar effects were observed on other lung function endpoints e.g. change from baseline in FVC at week 52 and FVC responder analyses providing further substantiation of the effects of nintedanib on slowing disease progression. See Figure 2 for the evolution of change from baseline over time in both treatment groups, based on the pooled analysis of studies INPULSIS-1 and INPULSIS-2.

Figure 2

Mean (SEM) observed FVC change from baseline (mL) over time, studies INPULSIS-1 and INPULSIS-2 pooled



#### FVC responder analysis

In both INPULSIS trials, the proportion of FVC responders, defined as patients with an absolute decline in FVC % predicted no greater than 5% (a threshold indicative of the increasing risk of mortality in IPF), was significantly higher in the nintedanib group as compared to placebo. Similar results were observed in analyses using a conservative threshold of 10%. See Table 7 for individual and pooled study results.

Table 7 Proportion of FVC responders at 52 weeks in trials INPULSIS-1, INPULSIS-2 and their pooled data - treated set

INPULSIS-1			INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
Placebo	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily	
Number of analysed patients	204	309	219	329	423	638
<b>5% threshold</b>						
Number (%) of FVC responders <sup>1</sup>	78 (38.2)	163 (52.8)	86 (39.3)	175 (53.2)	164 (38.8)	338 (53.0)
Comparison vs placebo						
Odds ratio	1.85		1.79		1.84	
95% CI	(1.28, 2.66)		(1.26, 2.55)		(1.43, 2.36)	
p-value <sup>2</sup>	0.0010		0.0011		<0.0001	
<b>10% threshold</b>						
Number (%) of FVC responders <sup>1</sup>	116 (56.9)	218 (70.6)	140 (63.9)	229 (69.6)	256 (60.5)	447 (70.1)
Comparison vs placebo						
Odds ratio	1.91		1.29		1.58	
95% CI	(1.32, 2.79)		(0.89, 1.86)		(1.21, 2.05)	
p-value <sup>2</sup>	0.0007		0.1833		0.0007	

<sup>1</sup>Responder patients are those with no absolute decline greater than 5% or greater than 10% in FVC %predicted, depending on the threshold and with an FVC evaluation at 52 weeks.  
<sup>2</sup>Based on a logistic regression

### Time to progression ( $\geq 10\%$ absolute decline of FVC % predicted or death)

In both INPULSIS trials, the risk of progression was statistically significantly reduced for patients treated with nintedanib compared with placebo. In the pooled analysis, the HR was 0.60 indicating a 40% reduction in the risk of progression for patients treated with nintedanib compared with placebo, see Table 8.

Table 8: Frequency of patients with  $\geq 10\%$  absolute decline of FVC % predicted or death over 52 weeks and time to progression in trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled	
	Placebo	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily
Number at risk	204	309	219	329	423	638
Patients with events, N (%)	83 (40.7)	75 (24.3)	92 (42.0)	98 (29.8)	175 (41.4)	173 (27.1)
Comparison vs placebo <sup>1</sup>						
p-value <sup>2</sup>		0.0001		0.0054		<0.0001
Hazard ratio <sup>3</sup>		0.53		0.67		0.60
95% CI		(0.39, 0.72)		(0.51, 0.89)		(0.49, 0.74)

<sup>1</sup> Based on data collected up to 372 days (52 weeks + 7 day margin).  
<sup>2</sup> Based on a Log-rank test.  
<sup>3</sup> Based on a Cox's regression model.

### Change from baseline in SGRQ total score at week 52

St. George's Respiratory Questionnaire (SGRQ) total score measuring health related quality of life (HRQoL) was analysed at 52 weeks. In INPULSIS-2, patients receiving placebo had a larger increase from baseline SGRQ total score as compared to patients receiving nintedanib 150 mg bid. The deterioration of HRQoL was smaller in the nintedanib group; the difference between the treatment groups was statistically significant (-2.69; 95% CI: -4.95, -0.43; p=0.0197).

In INPULSIS-1, the increase from baseline in SGRQ total score at week 52 was comparable between nintedanib and placebo (difference between treatment groups: -0.05; 95% CI: -2.50, 2.40; p=0.9657). In the pooled analysis of the INPULSIS trials, the estimated mean change from baseline to week 52 in SGRQ total score was smaller in the nintedanib group (3.53) than in the placebo group (4.96), with a difference between the treatment groups of -1.43 (95% CI: -3.09, 0.23; p = 0.0923). Overall, the effect of nintedanib on health-related quality of life as measured by the SGRQ total score is modest, indicating less worsening compared to placebo.

### Time to first acute IPF exacerbation

In the INPULSIS-2 trial, the risk of first acute IPF exacerbation over 52 weeks was significantly reduced in patients receiving nintedanib compared to placebo, in the INPULSIS-1 trial there was no difference in between the treatment groups. In the pooled analysis of the INPULSIS trials, a numerically lower risk of first acute exacerbation was observed in patients receiving nintedanib compared to placebo. See Table 9 for individual and pooled study results.

Table 9 Time to first acute exacerbation over 52 weeks based on investigator-reported events in trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 pooled		
	Placebo	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily
Number at risk	204	309	219	329	423	638
Patients with events, N (%)	11 (5.4)	19 (6.1)	21 (9.6)	12 (3.6)	32 (7.6)	31 (4.9)
Comparison vs placebo <sup>1</sup>						
p-value <sup>2</sup>		0.6728		0.0050		0.0823
Hazard ratio <sup>3</sup>		1.15		0.38		0.64
95% CI		(0.54, 2.42)		(0.19, 0.77)		(0.39, 1.05)

<sup>1</sup> Based on data collected up to 372 days (52 weeks + 7 day margin).  
<sup>2</sup> Based on a Log-rank test.  
<sup>3</sup> Based on a Cox's regression model

All adverse events of acute IPF exacerbation reported by the investigator were adjudicated by a blinded adjudication committee. A pre-specified sensitivity analysis of the time to first 'confirmed' or 'suspected' adjudicated acute IPF exacerbation was performed on the pooled data. The frequency of patients with at least 1 adjudicated exacerbation occurring within 52 weeks was lower in the nintedanib group (1.9% of patients) than in the placebo group (5.7% of patients). Time to event analysis of the adjudicated exacerbation events using pooled data yielded an HR of 0.32 (95% CI 0.16, 0.65; p = 0.0010). This indicates that the risk of having a first acute IPF exacerbation was statistically significantly lower in the nintedanib group than in the placebo group at any time point.

#### Survival analysis

In the pre-specified pooled analysis of survival data of the INPULSIS trials, overall mortality over 52 weeks was lower in the nintedanib group (5.5%) compared with the placebo group (7.8%). The analysis of time to death resulted in a HR of 0.70 (95% CI 0.43, 1.12; p = 0.1399). The results of all survival endpoints (such as on-treatment mortality and respiratory mortality) showed a consistent numerical difference in favour of nintedanib (see Table 10).

Table 10: All-cause mortality over 52 weeks in trials INPULSIS-1, INPULSIS-2, and their pooled data - treated set

	INPULSIS-1		INPULSIS-2		INPULSIS-1 and INPULSIS-2 Pooled	
	Placebo	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily	Placebo	Nintedanib Capsules 150 mg twice daily
Number at risk	204	309	219	329	423	638
Patients with events, N (%)	13 (6.4)	13 (4.2)	20 (9.1)	22 (6.7)	33 (7.8)	35 (5.5)
Comparison vs placebo <sup>1</sup>						

p-value <sup>2</sup>		0.2880		0.2995		0.1399
Hazard ratio <sup>3</sup>		0.63		0.74		0.70
95% CI		(0.29, 1.36)		(0.40, 1.35)		(0.43, 1.12)

<sup>1</sup> Based on data collected up to 372 days (52 weeks + 7 day margin).  
<sup>2</sup> Based on a Log-rank test.  
<sup>3</sup> Based on a Cox's regression model.

#### Supportive evidence from the phase II trial (1199.30) Nintedanib Capsules 150 mg twice daily results:

Additional evidence of efficacy is provided by the randomised, double-blind, placebo-controlled, dose finding phase II trial including a nintedanib 150 mg bid dose group. The primary endpoint, rate of decline in FVC over 52 weeks was lower in the nintedanib arm (-0.060 L/year, N=84) than the placebo arm (-0.190 L/year, N=83). The estimated difference between the treatment groups was 0.131 L/year (95% CI 0.027, 0.235). The difference between the treatment groups reached nominal statistical significance ( $p = 0.0136$ ). The estimated mean change from baseline in SGRQ total score at 52 weeks was 5.46 for placebo, indicating worsening of the health-related quality of life and -0.66 for nintedanib, indicating stable health-related quality of life. The estimated mean difference for nintedanib compared with placebo was -6.12 (95% CI: -10.57, -1.67;  $p = 0.0071$ ). The number of patients with acute IPF exacerbations over 52 weeks was lower in the nintedanib group (2.3%, N=86) compared to placebo (13.8%, N=87). The estimated hazard ratio of nintedanib versus placebo was 0.16 (95% CI 0.04, 0.71;  $p = 0.0054$ ).

Additional data from the phase IV INJOURNEY trial with CYENDIV® 150 mg twice daily and add-on pirfenidone:

Concomitant treatment with nintedanib and pirfenidone has been investigated in an exploratory open-label, randomised trial of nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times a day) compared to nintedanib 150 mg twice daily alone in 105 randomised patients for 12 weeks. The primary endpoint was the percentage of patients with gastrointestinal adverse events from baseline to week 12. Gastrointestinal adverse events were frequent and in line with the established safety profile of each component. Diarrhoea, nausea and vomiting were the most frequent adverse events reported in 20 (37.7%) versus 16 (31.4%), in 22 (41.5%) versus 6 (11.8%) and in 15 (28.3%) versus 6 (11.8%) patients, treated with pirfenidone added to nintedanib versus nintedanib alone, respectively.

Mean (SE) absolute changes from baseline in FVC at week 12 were -13.3 (17.4) mL in patients treated with nintedanib with add-on pirfenidone (n=48) compared to -40.9 (31.4) mL in patients treated with nintedanib alone (n=44).

#### Quality of Life

Treatment with nintedanib did not significantly change the time to deterioration of the pre-specified symptoms cough, dyspnoea and pain, but resulted in a significant deterioration in the diarrhoea symptom scale. Nevertheless, the overall treatment benefit of nintedanib was observed without adversely affecting self-reported quality of life..

#### Effect on QT interval

QT/QTc measurements were recorded and analysed from a dedicated study comparing nintedanib monotherapy against sunitinib monotherapy in patients with renal cell carcinoma. In this study single oral doses of 200 mg nintedanib as well as multiple oral doses of 200 mg nintedanib administered twice daily for 15 days did not prolong the QTcF interval.

However, no thorough QT-trial of nintedanib administered in combination with docetaxel was conducted.

### Paediatric studies

No clinical trials have been conducted in children and adolescents.

## **PHARMACOKINETICS**

The pharmacokinetics (PK) of nintedanib can be considered linear with respect to time (i.e. single-dose data can be extrapolated to multiple-dose data). Accumulation upon multiple administrations was 1.04-fold for  $C_{max}$  and 1.38-fold for  $AUC_{\tau}$ . Nintedanib trough concentrations remained stable for more than one year.

### Absorption

Nintedanib reached maximum plasma concentrations approximately 2 - 4 hours after oral administration as soft gelatin capsule under fed conditions (range 0.5 - 8 hours;). The absolute bioavailability of a 100 mg dose was 4.69 % (90 % CI: 3.615 - 6.078) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism.

Dose proportionality was shown by increase of nintedanib exposure (dose range 50 - 450 mg once daily and 150 - 300 mg twice daily). Steady state plasma concentrations were achieved within one week of dosing at the latest.

After food intake, nintedanib exposure increased by approximately 20 % compared to administration under fasted conditions (CI: 95.3 - 152.5 %) and absorption was delayed (median  $t_{max}$  fasted: 2.00 hours; fed: 3.98 h).

### Distribution

Nintedanib follows at least bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution ( $V_{ss}$  : 1050 L, 45.0 % gCV) was observed.

The *in vitro* protein binding of nintedanib in human plasma was high, with a bound fraction of 97.8 %. Serum albumin is considered to be the major binding protein. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.869.

### Metabolism

The prevalent metabolic reaction for nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by UGT enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide.

Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways, with CYP 3A4 being the predominant enzyme involved. The major CYP-dependent metabolite could not be detected in plasma in the human ADME study. *In vitro*, CYP-dependent metabolism accounted for about 5 % compared to about 25 % ester cleavage.

In preclinical *in vivo* experiments, BIBF 1202 did not show efficacy despite its activity at target receptors of the substance.

### Elimination

Total plasma clearance after intravenous infusion was high (CL: 1390 mL/min, 28.8 % gCV)

[58]. Urinary excretion of the unchanged active substance within 48 hours was about 0.05 % of dose (31.5 % gCV) after oral and about 1.4 % of the dose (24.2 % gCV) after intravenous administration; the renal clearance was 20 mL/min (32.6 % gCV). The major route of elimination of drug related radioactivity after oral administration of [<sup>14</sup>C] nintedanib was via faecal/biliary excretion (93.4 % of dose, 2.61 % gCV). The contribution of renal excretion to the total clearance was low (0.649 % of dose, 26.3 % gCV). The overall recovery was considered complete (above 90 %) within 4 days after dosing. The terminal half-life of nintedanib was between 10 and 15 h (gCV % approximately 50 %).

#### Exposure-response relationship

In exploratory pharmacokinetic( PK)-adverse event analyses, higher exposure to nintedanib tended to be associated with liver enzyme elevations, but not with gastrointestinal adverse events.

PK-efficacy analyses were not performed for clinical endpoints. Logistic regression revealed a statistically significant association between nintedanib exposure and DCE-MRI response

Exposure–response analyses indicated an  $E_{max}$ -like relationship between exposure in the range observed in Phase II and III and the annual rate of decline in FVC with an EC<sub>50</sub> of around 3-5 ng/mL (relative standard errors: 54-67%).

With respect to safety, there seemed to be a weak relationship between nintedanib plasma exposure and ALT and/or AST elevations. Actual administered dose might be the better predictor for the risk of developing diarrhoea of any intensity, even if plasma exposure as risk determining factor could not be ruled out. (see section *Special warnings and precautions*).

#### Intrinsic and Extrinsic Factors; Special Populations

The PK properties of nintedanib were similar in healthy volunteers, patients with IPF, and cancer patients. Based on results of Population PK (PopPK) analyses and descriptive investigations, exposure to nintedanib was not influenced by sex (body weight corrected), mild and moderate renal impairment (estimated by creatinine clearance), liver metastases, ECOG performance score, alcohol consumption, or P-gp genotype. Population PK analyses indicated moderate effects on exposure to nintedanib depending age, body weight and race (see below). Based on the high inter-individual variability of exposure observed in the clinical trials these effects are not considered clinically relevant. (see section *Special warnings and precautions*).

#### Age

Exposure to nintedanib increased linearly with age. AUC<sub>τ,ss</sub> decreased by 16 % for a 45-year old patient (5<sup>th</sup> percentile) and increased by 13 % for a 76-year old patient (95<sup>th</sup> percentile) relative to a patient with the median age of 62 years. The age range covered by the analysis was 29 to 85 years; approximately 5 % of the population was older than 75 years.  
Studies in paediatric populations have not been performed.

#### Body weight

An inverse correlation between body weight and exposure to nintedanib was observed. AUC<sub>τ,ss</sub> increased by 25 % for a 50 kg patient (5<sup>th</sup> percentile) and decreased by 19 % for a 100 kg patient (95<sup>th</sup> percentile) relative to a patient with the median weight of 71.5 kg.

## Race

The population mean exposure to nintedanib was 33 - 50 % higher in Chinese, Taiwanese, and Indian patients and 16 % higher in Japanese patients while it was 16 - 22 % lower in Koreans compared to Caucasians (body weight corrected).

Data from Black individuals was very limited but in the same range as for Caucasians.

## Hepatic impairment

In a dedicated single dose phase I study and compared to healthy subjects, exposure to nintedanib based on Cmax and AUC was 2.2-fold higher in volunteers with mild hepatic impairment (Child Pugh A; 90% CI 1.3 - 3.7 for Cmax and 1.2 - 3.8 for AUC, respectively). In volunteers with moderate hepatic impairment (Child Pugh B), exposure was 7.6-fold higher based on Cmax (90% CI 4.4 - 13.2) and 8.7-fold higher (90% CI 5.7 - 13.1) based on AUC, respectively, compared to healthy volunteers. Subjects with severe hepatic impairment (Child Pugh C) have not been studied.

## Concomitant treatment with pirfenidone

In a dedicated pharmacokinetic study, concomitant treatment of nintedanib with pirfenidone was investigated in patients with IPF. Group 1 received a single dose of 150 mg nintedanib before and after up titration to 801 mg pirfenidone three times a day at steady state. Group 2 received steady state treatment of 801 mg pirfenidone three times a day and had a PK profiling before and after at least 7 days of co-treatment with 150 mg nintedanib twice daily. In group 1, the adjusted geometric mean ratios (90% confidence interval (CI)) were 93% (57% - 151%) and 96% (70% - 131%) for Cmax and AUC<sub>0-tz</sub> of nintedanib, respectively (n=12). In group 2, the adjusted geometric mean ratios (90% CI) were 97% (86% - 110%) and 95% (86% - 106%) for Cmax,ss and AUC<sub>τ, ss</sub> of pirfenidone, respectively (n=12). Based on these results, there is no evidence of a relevant pharmacokinetic drug-drug interaction between nintedanib and pirfenidone when administered in combination

## Drug-Drug Interaction Potential

### Metabolism

Drug-drug interactions between nintedanib and CYP substrates, CYP inhibitors, or CYP inducers are not expected, since nintedanib, BIBF 1202, and BIBF 1202 glucuronide did not inhibit or induce CYP enzymes preclinically nor was nintedanib metabolized by CYP enzymes to a relevant extent.

### Transport

Nintedanib is a substrate of P-gp. For the interaction potential of nintedanib with this transporter, see section **Interactions**. Nintedanib was shown to be not a substrate or inhibitor of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2 or MRP-2 *in vitro*. Nintedanib was also not a substrate of BCRP. Only a weak inhibitory potential on OCT-1, BCRP, and P-gp was observed *in vitro* which is considered to be of low clinical relevance. The same applies for nintedanib being a substrate of OCT-1.

## **TOXICOLOGY**

### General toxicology

Single dose toxicity studies in rats and mice indicated a low acute toxic potential of

nintedanib. In repeat dose toxicology studies in rats, adverse effects (e.g. thickening of epiphyseal plates, lesions of the incisors) were mostly related to the mechanism of action (i.e. VEGFR-2 inhibition) of nintedanib. These changes are known from other VEGFR-2 inhibitors and can be considered class effects.

Diarrhoea and vomiting accompanied by reduced food consumption and loss of body weight were observed in toxicity studies in non-rodents.

There was no evidence of liver enzyme increases in rats, dogs, and Cynomolgus monkeys. Mild liver enzyme increases which were not due to serious adverse effects such as diarrhoea were only observed in Rhesus monkeys.

## Reproduction toxicity

A study of male fertility and early embryonic development up to implantation in rats did not reveal effects on the male reproductive tract and male fertility.

In rats, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure at the maximum recommended human dose (MRHD) 200 mg twice daily. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.

In rabbits, embryofoetal lethality and teratogenic effects comparable to those in rats were observed at an exposure slightly higher than in rats.

In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk ( $\leq 0.5\%$  of the administered dose).

From the 2-year carcinogenicity studies in mice and rats, there was no evidence for a carcinogenic potential of nintedanib.

Genotoxicity studies indicated no mutagenic potential for nintedanib.

A study of male fertility and early embryonic development up to implantation in rats did not reveal effects on the male reproductive tract and male fertility.

In rats, embryo-foetal lethality and teratogenic effects were observed at exposure levels below human exposure at the maximum recommended human dose (MRHD) of 150 mg twice daily. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.

In rabbits, embryofoetal lethality and teratogenic effects comparable to those in rats were observed at an exposure slightly higher than in rats

In rats, small amounts of radiolabelled nintedanib and/or its metabolites were excreted into the milk ( $\leq 0.5\%$  of the administered dose).

From the 2-year carcinogenicity studies in mice and rats, there was no evidence for a carcinogenic potential of nintedanib.

Genotoxicity studies indicated no mutagenic potential for nintedanib.

**Shelf life:** 36 Months

**Source:** 20180427

**Manufacturing Site:**

Catalent Germany Eberbach GmbH  
Gammelsbacher Str.2,  
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**Release Site:**

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Germany

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Bandra (East), Mumbai 400 051

**Storage-**

**Store at 2° to 8°C**

**Do not Freeze**

**Store in the original package in order to protect from moisture**

**Store in a safe place out of the reach of children.**

CYENDIV® India pack insert version dated 10<sup>th</sup> August 2018.

*For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only*

## Tacrolimus Capsule IP 0.5 mg, 1 mg, 5 mg

### **WARNING: MALIGNANCIES AND SERIOUS INFECTIONS**

- **Increased risk of development of lymphoma and other malignancies, particularly of the skin, due to immunosuppression.**
- **Increased susceptibility to bacterial, viral, fungal, and protozoal infections, including opportunistic infections.**
- **Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe tacrolimus. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.**

### **COMPOSITION**

Each hard gelatin capsule contains:

Tacrolimus IP.....0.5 mg/ 1 mg/ 5 mg

Excipients..... q.s.

Approved colours used in the capsule shell.

### **DESCRIPTION**

Tacrolimus is available for oral administration as capsules (tacrolimus capsules USP) containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus USP.

Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3S[3R\*[E(1S\*,3S\*,4S\*)], 4S\*,5R\*,8S\*,9E,12R\*,14R\*,15S\*,16R\*,18S\*,19S\*,26aR\*]]5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-15,19-epoxy-3H-pyrido[2,1-c][1,4] oxaazacyclotricosine-1,7,20,21(4H,23H)-tetrone, monohydrate.

Tacrolimus has an empirical formula of C<sub>44</sub>H<sub>69</sub>NO<sub>12</sub>•H<sub>2</sub>O and a formula weight of 822.03. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

### **CLINICAL PHARMACOLOGY**

#### **Mechanism of Action**

Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear

component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression).

## **Pharmacokinetics**

### **Absorption**

The rate and extent of absorption of tacrolimus is greatest under fasted conditions. The presence of food decreases both the rate and extent of absorption of tacrolimus. Bile flow does not influence the absorption of tacrolimus.

### **Distribution**

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration.

### **Metabolism**

Tacrolimus is widely metabolised in the liver, primarily by the cytochrome P450-3A4. Tacrolimus is also considerably metabolised in the intestinal wall. There are several metabolites identified. Only one of these has been shown in vitro to have immunosuppressive activity similar to that of tacrolimus. The other metabolites have only weak or no immunosuppressive activity. In systemic circulation only one of the inactive metabolites is present at low concentrations. Therefore, metabolites do not contribute to pharmacological activity of tacrolimus.

### **Excretion**

Following intravenous and oral administration of <sup>14</sup>C-labelled tacrolimus, most of the radioactivity was eliminated in the faeces. Approximately 2% of the radioactivity was eliminated in the urine. Less than 1% of unchanged tacrolimus was detected in the urine and faeces, indicating that tacrolimus is almost completely metabolised prior to elimination: bile being the principal route of elimination.

## **INDICATION**

For the prophylaxis of organ rejection in patients receiving allogenic liver, kidney or heart transplants.

It is recommended that tacrolimus be used concomitantly with azathioprine or mycophenolate mofetil (MMF) and adrenal corticosteroids.

## **DOSAGE AND ADMINISTRATION**

### **Dosage in Adult Kidney, Liver or Heart Transplant Patients**

The initial oral dosage recommendations for adult patients with kidney, liver, or heart transplants along with recommendations for whole blood trough concentrations are shown in table below.

Patient population	Recommended tacrolimus Initial Oral Dosage Note: daily doses should be administered as two divided doses, every 12 hours	Observed Tacrolimus Whole Blood Trough Concentrations

Adult kidney transplant patients  In combination with azathioprine	0.2 mg/kg/day	month 1-3: 7-20 ng/mL month 4-12: 5-15 ng/mL
In combination with MMF/IL-2 receptor antagonist <sup>a</sup>	0.1 mg/kg/day	month 1-12: 4-11 ng/mL
Adult liver transplant patients	0.10-0.15 mg/kg/day	month 1-12: 5-20 ng/mL
Adult heart transplant patients	0.075 mg/kg/day	month 1-3: 10-20 ng/mL month ≥4: 5-15 ng/mL

The initial dose of tacrolimus should be administered no sooner than 6 hours after transplantation in the liver and heart transplant patients. In kidney transplant patients, the initial dose of tacrolimus may be administered within 24 hours of transplantation, but should be delayed until renal function has recovered.

Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower tacrolimus dosages than the recommended initial dosage may be sufficient as maintenance therapy. Adjunct therapy with adrenal corticosteroids is recommended early post-transplant.

#### **Initial Dose – Injection**

In a patient receiving an IV infusion, the first dose of oral therapy should be given 8-12 hours after discontinuing the IV infusion.

The recommended starting dose of tacrolimus injection is 0.03-0.05 mg/kg/day in kidney and liver transplant and 0.01 mg/kg/day in heart transplant given as a continuous IV infusion. Adult patients should receive doses at the lower end of the dosing range. Concomitant adrenal corticosteroid therapy is recommended early post-transplantation.

#### **Paediatric population**

The initial oral dosage recommendations for pediatric patients with liver transplants along with recommendations for whole blood trough concentrations are shown below.

Patient population	Recommended tacrolimus initial oral dosage  Note: daily doses should be administered as two divided doses, every 12 hours.	Observed tacrolimus whole blood trough concentrations
Pediatric liver transplant patients	0.15-0.20 mg/kg/day	Month 1-12: 5-20 ng/mL

Pediatric liver transplantation patients without pre-existing renal or hepatic dysfunction have required and tolerated higher doses than adults to achieve similar blood concentrations.

Experience in pediatric kidney and heart transplantation patients is limited.

#### **CONTRAINDICATIONS**

Tacrolimus is contraindicated in patients with a hypersensitivity to tacrolimus. Hypersensitivity symptoms reported include dyspnea, rash, pruritus, and acute respiratory distress syndrome.

## **WARNINGS AND PRECAUTIONS**

### **Management of Immunosuppression**

Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should use tacrolimus. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physicians responsible for maintenance therapy should have complete information requisite for the follow up of the patient.

### **Lymphoma and Other Malignancies**

Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Post transplant lymphoproliferative disorder (PTLD) has been reported in immunosuppressed organ transplant recipients. The majority of PTLD events appear related to Epstein Barr Virus (EBV) infection. The risk of PTLD appears greatest in those individuals who are EBV seronegative, a population which includes many young children.

### **Serious Infections**

Patients receiving immunosuppressants, including vingraf, are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections. These infections may lead to serious, including fatal, outcomes. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

### **Polyoma Virus Infections**

Patients receiving immunosuppressants, including tacrolimus, are at increased risk for opportunistic infections, including polyoma virus infections. Polyoma virus infections in transplant patients may have serious, and sometimes fatal, outcomes. These include polyoma virus-associated nephropathy (PVAN), mostly due to BK virus infection, and JC virus-associated progressive multifocal leukoencephalopathy (PML) which have been observed in patients receiving tacrolimus. PVAN is associated with serious outcomes, including deteriorating renal function and kidney graft loss. Patient monitoring may help detect patients at risk for PVAN. Cases of PML have been reported in patients treated with tacrolimus. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated.

Reductions in immunosuppression should be considered for patients who develop evidence of PVAN or PML. Physicians should also consider the risk that reduced immunosuppression represents to the functioning allograft.

### **Cytomegalovirus (CMV) Infections**

Patients receiving immunosuppressants, including tacrolimus, are at increased risk of developing CMV viremia and CMV disease. The risk of CMV disease is highest among transplant recipients seronegative for CMV at time of transplant who receive a graft from a

CMV seropositive donor. Therapeutic approaches to limiting CMV disease exist and should be routinely provided. Patient monitoring may help detect patients at risk for CMV disease. Consideration should be given to reducing the amount of immunosuppression in patients who develop CMV viremia and/or CMV disease.

### **New Onset Diabetes After Transplant**

Tacrolimus was shown to cause new onset diabetes mellitus in clinical trials of kidney, liver, and heart transplantation. New onset diabetes after transplantation may be reversible in some patients. Blood glucose concentrations should be monitored closely in patients using tacrolimus.

### **Nephrotoxicity**

Tacrolimus, like other calcineurin-inhibitors, can cause acute or chronic nephrotoxicity, particularly when used in high doses. Acute nephrotoxicity is most often related to vasoconstriction of the afferent renal arteriole, is characterized by increasing serum creatinine, hyperkalemia, and/or a decrease in urine output, and is typically reversible. Chronic calcineurin inhibitor nephrotoxicity is associated with increased serum creatinine, decreased kidney graft life, and characteristic histologic changes observed on renal biopsy; the changes associated with chronic calcineurin-inhibitor nephrotoxicity are typically progressive. Patients with impaired renal function should be monitored closely as the dosage of tacrolimus may need to be reduced. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy.

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering tacrolimus with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, ganciclovir, amphotericin B, cisplatin, nucleotide reverse transcriptase inhibitors (e.g., tenofovir) and protease inhibitors (e.g., ritonavir, indinavir). Similarly, care should be exercised when administering with CYP3A4 inhibitors such as antifungal drugs (e.g., ketoconazole), calcium channel blockers (e.g., diltiazem, verapamil), and macrolide antibiotics (e.g., clarithromycin, erythromycin, troleandomycin) which will result in increased tacrolimus whole blood concentrations due to inhibition of tacrolimus metabolism.

### **Neurotoxicity**

Tacrolimus may cause a spectrum of neurotoxicities, particularly when used in high doses. The most severe neurotoxicities include posterior reversible encephalopathy syndrome (PRES), delirium, and coma. Patients treated with tacrolimus have been reported to develop PRES. Symptoms indicating PRES include headache, altered mental status, seizures, visual disturbances and hypertension. Diagnosis may be confirmed by radiological procedure. If PRES is suspected or diagnosed, blood pressure control should be maintained and immediate reduction of immunosuppression is advised. This syndrome is characterized by reversal of symptoms upon reduction or discontinuation of immunosuppression. Coma and delirium, in the absence of PRES, have also been associated with high plasma concentrations of tacrolimus. Seizures have occurred in adult and pediatric patients receiving tacrolimus. Less severe neurotoxicities, include tremors, parathesias, headache, and other changes in motor function, mental status, and sensory function. Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment.

### **Hyperkalemia**

Hyperkalemia has been reported with tacrolimus use. Serum potassium levels should be monitored. Careful consideration should be given prior to use of other agents also associated with hyperkalemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers) during tacrolimus therapy.

### **Hypertension**

Hypertension is a common adverse effect of tacrolimus therapy and may require antihypertensive therapy. The control of blood pressure can be accomplished with any of the common antihypertensive agents, though careful consideration should be given prior to use of antihypertensive agents associated with hyperkalemia (e.g., potassium-sparing diuretics, ACE inhibitors, angiotensin receptor blockers). Calcium-channel blocking agents may increase tacrolimus blood concentrations and therefore require dosage reduction of tacrolimus.

### **Use with Sirolimus**

The safety and efficacy of tacrolimus with sirolimus has not been established in kidney transplant patients.

Use of sirolimus with tacrolimus in studies of *de novo* liver transplant patients was associated with an excess mortality, graft loss, and hepatic artery thrombosis (HAT) and is not recommended. Use of sirolimus (2 mg per day) with tacrolimus in heart transplant patients was associated with increased risk of renal function impairment, wound healing complications, and insulin-dependent post-transplant diabetes mellitus, and is not recommended.

### **Use with Strong Inhibitors and Inducers of CYP3A**

Co-administration with strong CYP3A4-inhibitors (e.g., ritonavir, ketoconazole, itraconazole, voriconazole, clarithromycin) and strong inducers (e.g., rifampin, rifabutin) is not recommended without close monitoring of tacrolimus whole blood trough concentrations.

### **Myocardial Hypertrophy**

Myocardial hypertrophy has been reported in infants, children, and adults, particularly those with high tacrolimus trough concentrations, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. This condition appears reversible in most cases following dose reduction or discontinuance of therapy. In patients who develop renal failure or clinical manifestations of ventricular dysfunction while receiving tacrolimus therapy, echocardiographic evaluation should be considered. If myocardial hypertrophy is diagnosed, dosage reduction or discontinuation of tacrolimus should be considered.

### **Immunizations**

The use of live vaccines should be avoided during treatment with tacrolimus; examples include (not limited to) the following: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

### **Pure Red Cell Aplasia**

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with tacrolimus. A mechanism for tacrolimus-induced PRCA has not been elucidated. All patients reported risk factors for PRCA such as parvovirus B19 infection, underlying disease, or concomitant medications associated with PRCA. If PRCA is diagnosed, discontinuation of tacrolimus should be considered.

## **ADVERSE REACTIONS**

Adverse drug reactions are listed below in descending order by frequency of occurrence: very common ( $\geq 1/10$ ); common ( $\geq 1/100, < 1/10$ ); uncommon ( $\geq 1/1,000, < 1/100$ ).

**Very common:** hyperglycaemic conditions, diabetes mellitus, hyperkalaemia, insomnia, tremor, headache, hypertension, diarrhoea, nausea, renal impairment

**Common:** anaemia, leukopenia, thrombocytopenia, leukocytosis, red blood cell analyses abnormal, hypomagnesaemia, hypophosphataemia, hypokalaemia, hypocalcaemia, hyponatraemia, fluid overload, hyperuricaemia, appetite decreased, metabolic acidoses, hyperlipidaemia, hypercholesterolaemia, hypertriglyceridaemia, other electrolyte abnormalities, anxiety symptoms, confusion and disorientation, depression, depressed mood, mood disorders and disturbances, nightmare, hallucination, mental disorders, seizures, disturbances in consciousness, paraesthesia and dysaesthesia, peripheral neuropathies, dizziness, writing impaired, nervous system disorders, vision blurred, photophobia, eye disorders, tinnitus, ischaemic coronary artery disorders, tachycardia, haemorrhage, thrombembolic and ischaemic events, peripheral vascular disorders, vascular hypotensive disorders, dyspnoea, parenchymal lung disorders, pleural effusion, pharyngitis, cough, nasal congestion and inflammations, gastrointestinal inflammatory conditions, gastrointestinal ulceration and perforation, gastrointestinal haemorrhages, stomatitis and ulceration, ascites, vomiting, gastrointestinal and abdominal pains, dyspeptic signs and symptoms, constipation, flatulence, bloating and distension, loose stools, gastrointestinal signs and symptoms, cholestasis and jaundice, hepatocellular damage and hepatitis, cholangitis, pruritus, rash, alopecias, acne, sweating increased, arthralgia, muscle spasms, pain in limb, back pain, renal failure, renal failure acute, oliguria, renal tubular necrosis, nephropathy, toxic, urinary abnormalities, bladder and urethral symptoms, asthenic conditions, febrile disorders, oedema, pain and discomfort, body temperature perception disturbed, hepatic enzymes and function abnormalities, blood alkaline phosphatase, increased, weight increased, primary graft dysfunction

**Uncommon:** coagulopathies, coagulation and bleeding analyses abnormal, pancytopenia, neutropenia, dehydration, hypoproteinaemia, hyperphosphataemia, hypoglycaemia, psychotic disorder, coma, central nervous system haemorrhages and cerebrovascular accidents, paralysis and paresis, encephalopathy, speech and language abnormalities, amnesia, cataract, hypoacusis, ventricular arrhythmias and cardiac arrest, heart failures, cardiomyopathies, ventricular hypertrophy, supraventricular arrhythmias, palpitations, infarction, venous thrombosis deep limb, shock Respiratory, thoracic and mediastinal disorders, ileus paralytic, acute and chronic pancreatitis, gastrooesophageal reflux disease, impaired gastric emptying, dermatitis, photosensitivity, joint disorders, anuria, haemolytic uraemic syndrome, dysmenorrhoea and uterine bleeding, multi-organ failure, influenza like illness, temperature intolerance, chest pressure sensation, feeling jittery, feeling abnormal, amylase increased, ECG investigations abnormal, heart rate and pulse investigations abnormal, weight decreased, blood lactate dehydrogenase increased

## DRUG INTERACTIONS

Since tacrolimus is metabolized mainly by CYP3A enzymes, drugs or substances known to inhibit these enzymes may increase tacrolimus whole blood concentrations. Drugs known to induce CYP3A enzymes may decrease tacrolimus whole blood concentrations.

### Mycophenolic Acid Products

With a given dose of mycophenolic acid (MPA) products, exposure to MPA is higher with tacrolimus co-administration than with cyclosporine co-administration because cyclosporine

interrupts the enterohepatic recirculation of MPA while tacrolimus does not. Clinicians should be aware that there is also a potential for increased MPA exposure after crossover from cyclosporine to tacrolimus in patients concomitantly receiving MPA-containing products.

### **Grapefruit Juice**

Grapefruit juice inhibits CYP3A-enzymes resulting in increased tacrolimus whole blood trough concentrations, and patients should avoid eating grapefruit or drinking grapefruit juice with tacrolimus.

### **Protease Inhibitors**

Most protease inhibitors inhibit CYP3A enzymes and may increase tacrolimus whole blood concentrations. It is recommended to avoid concomitant use of tacrolimus with nelfinavir unless the benefits outweigh the risks. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when tacrolimus and other protease inhibitors (e.g., ritonavir) are used concomitantly.

### **Antifungal Agents**

Frequent monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when concomitant use of the following antifungal drugs with tacrolimus is initiated or discontinued.

Azoles: Voriconazole, posaconazole, itraconazole, ketoconazole, fluconazole and clotrimazole inhibit CYP3A metabolism of tacrolimus and increase tacrolimus whole blood concentrations. When initiating therapy with voriconazole or posaconazole in patients already receiving tacrolimus, it is recommended that the tacrolimus dose be initially reduced to one-third of the original dose and the subsequent tacrolimus doses be adjusted based on the tacrolimus whole blood concentrations.

Caspofungin is an inducer of CYP3A and decreases whole blood concentrations of tacrolimus.

### **Calcium Channel Blockers**

Verapamil, diltiazem, nifedipine, and nicardipine inhibit CYP3A metabolism of tacrolimus and may increase tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these calcium channel blocking drugs and tacrolimus are used concomitantly.

### **Antibacterials**

Erythromycin, clarithromycin, troleandomycin and chloramphenicol inhibit CYP3A metabolism of tacrolimus and may increase tacrolimus whole blood concentrations. Monitoring of blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly.

### **Antimycobacterials**

Rifampin and rifabutin are inducers of CYP3A enzymes and may decrease tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these anti-mycobacterial drugs and tacrolimus are used concomitantly.

### **Anticonvulsants**

Phenytoin, carbamazepine and phenobarbital induce CYP3A enzymes and may decrease tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly.

Concomitant administration of phenytoin with tacrolimus may also increase phenytoin plasma concentrations. Thus, frequent monitoring phenytoin plasma concentrations and adjusting the

phenytoin dose as needed are recommended when tacrolimus and phenytoin are administered concomitantly.

#### **St. John's Wort (*Hypericum perforatum*)**

St. John's Wort induces CYP3A enzymes and may decrease tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when St. John's Wort and tacrolimus are co-administered.

#### **Gastric Acid Suppressors/Neutralizers**

Lansoprazole and omeprazole, as CYP2C19 and CYP3A4 substrates, may potentially inhibit the CYP3A4 metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations, especially in transplant patients who are intermediate or poor CYP2C19 metabolizers, as compared to those patients who are efficient CYP2C19 metabolizers.

Cimetidine may also inhibit the CYP3A4 metabolism of tacrolimus and thereby substantially increase tacrolimus whole blood concentrations. Coadministration with magnesium and aluminum hydroxide antacids increase tacrolimus whole blood concentrations. Monitoring of whole blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are used concomitantly.

#### **Others**

Bromocriptine, nefazodone, metoclopramide, danazol, ethinyl estradiol and methylprednisolone may inhibit CYP3A metabolism of tacrolimus and increase tacrolimus whole blood concentrations. Monitoring of blood concentrations and appropriate dosage adjustments of tacrolimus are recommended when these drugs and tacrolimus are co-administered.

### **USE IN SPECIAL POPULATION**

#### **Pregnancy Category C**

Tacrolimus should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus

#### **Lactation**

Tacrolimus is excreted in human milk. As the effect of chronic exposure to tacrolimus in healthy infants is not established, patients maintained on tacrolimus should discontinue nursing taking into consideration importance of drug to the mother.

#### **Pediatric use:**

The safety and efficacy of tacrolimus in pediatric kidney and heart transplant patients have not been established. Successful liver transplants have been performed in pediatric patients (ages up to 16 years) using tacrolimus.

#### **Geriatric use**

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

#### **Hepatic impairment**

The mean clearance of tacrolimus was substantially lower in patients with severe hepatic impairment (mean Child-Pugh score: >10) compared to healthy volunteers with normal hepatic function. Close monitoring of tacrolimus trough concentrations is warranted in patients with hepatic impairment.

#### **Renal impairment**

Consideration should be given to dose tacrolimus at the lower end of the therapeutic dosing range in patients who have received a liver or heart transplant and have pre-existing renal impairment. Further reductions in dose below the targeted range may be required

## **OVERDOSAGE**

Limited overdosage experience is available. Acute overdosages of up to 30 times the intended dose have been reported. Almost all cases have been asymptomatic and all patients recovered with no sequelae. Acute overdosage was sometimes followed by adverse reactions including tremors, abnormal renal function, hypertension, and peripheral edema); in one case of acute overdosage, transient urticaria and lethargy were observed. Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent; there is no experience with charcoal hemoperfusion. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of over dosage.

## **STORAGE**

Store Protected from moisture at a temperature not exceeding 30<sup>0</sup>c.

## **PRESENTATION**

Tacrolimus Capsules IP 0.5 mg – 6 X 10 Capsules

Tacrolimus Capsules IP 1 mg – 6 X 10 Capsules

Tacrolimus Capsules IP 5 mg – 1 X 10 Capsules

## Topotecan Hydrochloride for Injection

### HYCAMTIN®

Antineoplastic agents.

### DESCRIPTION AND COMPOSITION

#### Pharmaceutical form

A sterile, lyophilized powder in single-dose vials for intravenous (i.v.) infusion following reconstitution and further dilution.

Powder for solution for infusion, 1 mg and 4 mg.

Each 1 mg vial contains 1 mg topotecan as topotecan hydrochloride, with a 10% overage of fill.

Each 4 mg vial contains 4 mg topotecan as topotecan hydrochloride.

Certain dosage strengths may not be available in all countries.

#### Active Moiety

Topotecan hydrochloride.

#### Excipients

Tartaric acid (Ph Eur), Mannitol (Ph Eur), Hydrochloric acid (Ph Eur), Sodium hydroxide (Ph Eur).

### INDICATIONS

*HYCAMTIN* is indicated for the treatment of:

- Metastatic ovarian cancer after failure of first line chemotherapy.
- Small cell lung cancer sensitive disease after failure of first-line chemotherapy. In clinical studies submitted to support approval, sensitive disease was defined as disease responding to chemotherapy but subsequently progressing at least 60 days (in the Phase 3 study) or at least 90 days (in the Phase 2 studies) after chemotherapy.
- *HYCAMTIN* in combination with cisplatin is indicated for the treatment of patients with histologically confirmed Stage IV-B, recurrent, or persistent carcinoma of the cervix, which is not amenable to curative treatment with surgery and/or radiation therapy.

For efficacy data see Clinical Studies.

### DOSAGE REGIMEN AND ADMINISTRATION

Hycamtin must be reconstituted and further diluted before use (see section INSTRUCTIONS FOR USE AND HANDLING).

Prior to administration of the first course of Hycamtin, patients must have a baseline neutrophil count of more than or equal to  $1.5 \times 10^9/L$ , a platelet count of more than or equal to  $100 \times 10^9/L$  and a hemoglobin level of more than or equal to 9 g/dL (after transfusion if necessary).

## **Populations - Adults and Elderly**

### **Ovarian and small cell lung carcinoma Initial dose**

The recommended dose of Hycamtin is 1.5 mg/m<sup>2</sup> by intravenous infusion over 30 minutes daily for 5 consecutive days, starting on day 1 of a 21-day course. In the absence of tumor progression, a minimum of 4 courses is recommended because tumor response may be delayed. The median time to response in three ovarian clinical trials was 7.6 to 11.7 weeks and median time to response in four small cell lung cancer trials was 6.1 weeks.

### **Subsequent doses**

Hycamtin should not be re-administered unless the neutrophil count is more than or equal to 1 x 10<sup>9</sup>/L, the platelet count is more than or equal to 100 x 10<sup>9</sup>/L, and the hemoglobin level is more than or equal to 9 g/dL (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer Hycamtin with other medications (e.g. G-CSF) or to reduce the dose to maintain neutrophil counts.

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count less than or equal to 0.5 x 10<sup>9</sup>/L) for 7 days or more, or severe neutropenia associated with fever or infection, or who have had treatment delayed due to neutropenia, the dose should be reduced by 0.25 mg/m<sup>2</sup>/day to 1.25 mg/m<sup>2</sup>/day (or subsequently down to 1.0 mg/m<sup>2</sup>/day if necessary).

Doses should be similarly reduced if the platelet count falls below 25 x 10<sup>9</sup>/L.

In clinical trials, topotecan powder for i.v. infusion was discontinued if the dose had to be reduced below 1.0 mg/m<sup>2</sup>.

## **Cervical Cancer**

### **Initial dose**

The recommended dose of Hycamtin is 0.75 mg/m<sup>2</sup> administered as a 30 minute intravenous infusion daily on days 1, 2 and 3. Cisplatin is administered as an intravenous infusion on day 1 at a dose of 50 mg/m<sup>2</sup> and following the Hycamtin dose. This treatment schedule is repeated every 21 days for 6 courses or until disease progression.

### **Subsequent doses**

Hycamtin should not be re-administered unless the neutrophil count is more than or equal to 1.5 x 10<sup>9</sup>/L, the platelet count is more than or equal to 100 x 10<sup>9</sup>/L, and the haemoglobin level is more than or equal to 9 g/dL (after transfusion if necessary).

Standard oncology practice for the management of neutropenia is either to administer Hycamtin with other medications (e.g. G-CSF) or to reduce the dose to maintain neutrophil counts.

If dose reduction is chosen for patients who experience severe neutropenia (neutrophil count less than 0.5 x 10<sup>9</sup>/L) for 7 days or more, or severe neutropenia associated with fever or infection or who have had treatment delayed due to neutropenia, the dose should be reduced by 20% to 0.60 mg/m<sup>2</sup> for subsequent courses (or subsequently down to 0.45 mg/m<sup>2</sup>/day).

Doses should be similarly reduced if the platelet count falls below 25 x 10<sup>9</sup>/L.

## **Dosage in Combination**

Dose adjustment may be necessary if Hycamtin is administered in combination with other cytotoxic agents (see section INTERACTIONS).

## **Special Populations**

### **Pediatric patients (below 18 years)**

Due to limited data on efficacy and safety in the paediatric population, no recommendation for treatment of children with Hycamtin can be given.

### **Geriatric patients (65 years or above)**

No dosage adjustment appears to be needed in the elderly, other than adjustments related to renal function.

### **Renal impairment**

#### **Monotherapy**

No dosage adjustment appears to be required for treating patients with mild renal impairment (creatinine clearance 40 to 60 mL/min.). Dosage adjustment to 0.75 mg/m<sup>2</sup> is recommended for patients with a creatinine clearance of 20 to 39 mL/min. Insufficient data are available in patients with severe renal impairment to provide a dosage recommendation. Advice on dosing of Hycamtin for patients with moderate renal impairment (20 to 39 mL/min) is based on studies involving patients with advanced cancer.

#### **Combination therapy**

It is recommended that Hycamtin in combination with cisplatin for the treatment of cervical cancer only be initiated in patients with serum creatinine less than or equal to 1.5 mg/dL. If, during Hycamtin/cisplatin combination therapy serum creatinine exceeds 1.5 mg/dL, it is recommended that the full prescribing information be consulted for any advice on cisplatin dose reduction/continuation. If cisplatin is discontinued, there are insufficient data regarding continuing monotherapy with topotecan in patients with cervical cancer.

### **Hepatic impairment**

#### **Monotherapy**

No dosage adjustment appears to be required for treating patients with impaired hepatic function (serum bilirubin in the range 1.5 to 10 mg/dL).

## **CONTRAINDICATIONS**

Hycamtin is contra-indicated in patients who

- have a history of severe hypersensitivity reactions to topotecan and/or its excipients
- are pregnant or breast-feeding (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL)
- already have severe bone marrow depression prior to starting first course, as evidenced by baseline neutrophils less than 1.5 x 10<sup>9</sup>/L and/or a platelet count of less than 100 x 10<sup>9</sup>/L.

## **WARNINGS AND PRECAUTIONS**

Hycamtin should be initiated under the direction of a physician experienced in the use of cytotoxic agents.

Hematological toxicity is dose-related and full blood count including platelets should be monitored regularly (see section DOSAGE REGIMEN AND ADMINISTRATION).

As with other cytotoxic drugs, Hycamtin can cause severe myelosuppression. Myelosuppression leading to sepsis and fatalities due to sepsis have been reported in patients treated with Hycamtin (see section ADVERSE DRUG REACTIONS).

Topotecan-induced neutropenia can cause neutropenic colitis. Fatalities due to neutropenic colitis have been reported in clinical trials with topotecan. In patients presenting with fever, neutropenia, and a compatible pattern of abdominal pain, the possibility of neutropenic colitis should be considered.

Hycamtin has been associated with reports of interstitial lung disease (ILD), some of which have been fatal (see section ADVERSE DRUG REACTIONS). Underlying risk factors include history of ILD, pulmonary fibrosis, lung cancer, thoracic exposure to radiation and use of pneumotoxic drugs and/or colony stimulating factors. Patients should be monitored for pulmonary symptoms indicative of ILD (e.g. cough, fever, dyspnea and/or hypoxia), and Hycamtin should be discontinued if a new diagnosis of ILD is confirmed.

Dose adjustment may be necessary if Hycamtin is administered in combination with other cytotoxic agents (see section INTERACTIONS).

## **Driving and using machines**

Caution should be observed when driving or operating machinery if fatigue and asthenia persist.

## **ADVERSE DRUG REACTIONS**

In the intravenous topotecan studies for treatment of ovarian cancer, prolonged use (more than six courses) of topotecan was not associated with an increase in the rate of haematologic toxicity.

The following frequencies are estimated at the standard recommended doses of topotecan according to indication and formulation.

Further information regarding incidence and grade of toxicity is presented in the Clinical Studies section.

Adverse drug reactions from clinical trials (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $<1/10$ ); uncommon ( $\geq 1/1,000$  to  $<1/100$ ); rare ( $\geq 1/10,000$  to  $<1/1,000$ ); very rare ( $<1/10,000$ ), not known (cannot be estimated from the available data).

**Table 1 Percentage of patients with adverse drug reactions in clinical trials**

### **Infections and infestations**

Very Common	Infection
Common	Sepsis (see section WARNINGS AND PRECAUTIONS)

### **Blood and lymphatic system disorders**

Very Common	Anaemia, febrile neutropenia, leucopenia, neutropenia <sup>2</sup> (see Gastrointestinal disorders), thrombocytopenia
Common	Pancytopenia

### **Immune system disorders**

Common	Hypersensitivity, including rash
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### **Metabolism and nutrition disorders**

Very Common	Anorexia (which may be severe)
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### **Respiratory, thoracic and mediastinal disorders**

Rare	Interstitial lung disease
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### **Gastrointestinal disorders**

Very Common	Diarrhoea <sup>1</sup> (see section WARNINGS AND PRECAUTIONS), nausea and vomiting (all of which may be severe), abdominal pain <sup>2</sup> , constipation and stomatitis.
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### **Hepatobiliary disorders**

Common	Hyperbilirubinaemia
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### **Skin and subcutaneous disorders**

Very Common	Alopecia
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### **General disorders and administrative site conditions**

Very Common	Asthenia, fatigue, pyrexia
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Common	Malaise
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Very Rare	Extravasation <sup>3</sup> (i.v. formulation only)
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<sup>1</sup>With oral topotecan the overall incidence of drug-related diarrhea was 22%, including 4% with Grade 3 and 0.4% with Grade 4. With oral topotecan, drug-related diarrhea was more frequent in patients greater than or equal to 65 years of age (28%) compared to those less than 65 years of age (19%). After I.V. topotecan, drug-related diarrhea in patients greater than 65 years of age was 10%.

<sup>2</sup>Neutropenic colitis, including fatal neutropenic colitis, has been reported to occur as a complication of topotecan-induced neutropenia (see section WARNINGS AND PRECAUTIONS).

<sup>3</sup>Reactions associated with extravasation have been mild and have not generally required specific therapy.

## **Adverse drug reactions from spontaneous reports and literature cases (frequency not known)**

The following adverse drug reactions have been derived from post-marketing experience with Hycamtin via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency, which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

**Table 1 Adverse drug reactions from spontaneous reports and literature (frequency not known)**

### **Blood and lymphatic system disorders**

Severe bleeding (associated with thrombocytopenia) (see section WARNINGS AND PRECAUTIONS)

### **Immune system disorders**

Anaphylactic reaction

### **Gastrointestinal disorders**

Gastrointestinal perforation

### **General disorders and administration site conditions**

Mucosal inflammation

### **Gastrointestinal disorders**

Gastrointestinal perforation

### **General disorders and administration site conditions**

Mucosal inflammation

## **INTERACTIONS**

As with other myelosuppressive cytotoxic agents, greater myelosuppression is likely to be seen when Hycamtin is used in combination with other cytotoxic agents (e.g. paclitaxel or etoposide) thereby necessitating dose reduction. However, in combining with platinum agents (e.g. cisplatin or carboplatin), there is a distinct sequence-dependent interaction depending on whether the platinum agent is given on day 1 or 5 of the topotecan dosing. If the platinum agent is given on day 1 of the topotecan dosing, lower doses of each agent must be given compared to the doses which can be given if the platinum agent is given on day 5 of the topotecan dosing (see section DOSAGE REGIMEN AND ADMINISTRATION).

When topotecan (0.75 mg/m<sup>2</sup>/day for five consecutive days) and cisplatin (60 mg/m<sup>2</sup>/day on Day 1) were administered intravenously in 13 patients with ovarian cancer, mean topotecan plasma clearance on Day 5 was slightly reduced compared to values on Day 1. As a result, systemic exposure of total topotecan, as measured by AUC and C<sub>max</sub>, on Day 5 were increased by 12% (95% CI; 2%, 24%) and 23% (95% CI; —7%, 63%), respectively. No pharmacokinetic data are available following topotecan (0.75 mg/m<sup>2</sup>/day for three consecutive days) and cisplatin (50 mg/m<sup>2</sup>/day on Day 1) in patients with cervical cancer.

Topotecan does not inhibit human cytochrome P450 enzymes (see section PHARMACOKINETICS). In population studies, the co-administration (in separate lines or by separate routes) of granisetron, ondansetron, morphine or corticosteroids did not appear to have a significant effect on the pharmacokinetics of intravenously administered topotecan.

Topotecan is a substrate for both ABCG2 (BCRP) and ABCB1 (P-glycoprotein). Inhibitors of ABCB1 and ABCG2 (e.g. elacridar) administered with oral topotecan increased topotecan exposure. The effect of elacridar on the pharmacokinetics of intravenous topotecan was much less than the effect on oral topotecan.

## PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

### Pregnancy

#### Risk summary

Hycamtin is contraindicated during pregnancy (see section CONTRAINDICATIONS).

Based on animal data, Hycamtin can cause fetal harm when administered to a pregnant woman. Topotecan caused embryotoxicity, fetotoxicity, and teratogenicity when administered in rats and rabbits at doses lower than the clinical dose [see Animal data].

#### Animal data

As with other cytotoxic agents, topotecan was also shown to cause embryo-fetal toxicity when given to rats ( $0.59 \text{ mg/m}^2/\text{day}$ ) and rabbits ( $1.25 \text{ mg/m}^2/\text{day}$ ) at doses less than the clinical i.v. dose in humans ( $1.5 \text{ mg/m}^2/\text{day}$ ). A dose of  $0.59 \text{ mg/m}^2$  was teratogenic in rats (predominantly effects of the eye, brain, skull and vertebrae).

### Lactation

#### Risk summary

Hycamtin is contra-indicated during breast-feeding (see section CONTRAINDICATION).

It is not known whether this drug is present in human milk; however, topotecan is transferred into rat milk at high concentrations [see Animal data]. Because of the potential for serious adverse reactions in nursing infants with topotecan, nursing mothers should be advised to discontinue breastfeeding during treatment with Hycamtin.

### Animal Data

Following intravenous administration of topotecan to lactating rats at a dose of  $4.72 \text{ mg/m}^2$  (about twice the clinical dose on a  $\text{mg/m}^2$  basis), topotecan was transferred into milk at concentrations up to 48-fold higher than those in plasma. The concentration in milk declined to 2-fold higher than that in plasma at 72 h.

### Females and males of reproductive potential

Females of reproductive potential should be advised to avoid becoming pregnant during therapy with Hycamtin and to inform the treating physician immediately should this occur.

### Pregnancy testing

Pregnancy status should be verified for females of reproductive potential prior to starting treatment with Hycamtin.

### Contraception

Females:

As with all cytotoxic drugs, females of reproductive potential should use effective contraception (methods that result in less than 1 % pregnancy rates) during treatment with Hycamtin

Males:

Because of genotoxic potential, male patients should use condoms during sexual intercourse while taking Hycamtin and for at least 3 months after stopping treatment with Hycamtin.

### Infertility

No effects on male or female fertility have been observed in reproductive toxicity studies in rats (see section NON-CLINICAL SAFETY DATA). However, as with other cytotoxic medicinal products, topotecan is genotoxic and effects on fertility, including male fertility, cannot be excluded.

## **OVERDOSAGE**

### **Symptoms and Signs**

Overdoses (up to 10 fold of the prescribed dose) have been reported in patients being treated with intravenous topotecan. The primary complication of overdosage is bone marrow suppression. The observed signs and symptoms for overdose are consistent with the known adverse reactions associated with topotecan (see section ADVERSE DRUG REACTIONS). In addition, elevated hepatic enzymes and mucositis have been reported following overdose.

### **Treatment**

There is no known antidote for topotecan overdosage. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

## **CLINICAL PHARMACOLOGY**

### **Pharmacodynamics**

#### **Mechanism of Action**

The anti-tumor activity of topotecan involves the inhibition of topoisomerase-I, an enzyme intimately involved in DNA replication as it relieves the torsional strain introduced ahead of the moving replication fork. Topotecan inhibits topoisomerase-I by stabilising the covalent complex of enzyme and strand-cleaved DNA which is an intermediate of the catalytic mechanism. The cellular sequelae of inhibition of topoisomerase-I by topotecan is the induction of protein-associated DNA single-strand breaks.

### **Pharmacokinetics**

#### **Absorption**

Not applicable for i.v.

#### **Distribution**

Topotecan has a high volume of distribution of about 132 L, approximately three times total body water, and a relatively short half-life of two to three hours. Comparison of pharmacokinetic parameters did not suggest any change in pharmacokinetics over the five days of dosing.

The binding of topotecan to plasma proteins was low (35%) and distribution between blood cells and plasma was homogeneous.

Plasma clearance and volume of distribution were found to be slightly higher in males than females. However, differences were found to be similar in magnitude to differences in body surface area.

#### **Metabolism**

A major route of inactivation of topotecan is a reversible pH-dependent ring opening to the inactive carboxylate form.

Metabolism accounts for less than 10% of the elimination of topotecan. A N-desmethyl metabolite was found in urine, plasma, and faeces. Following oral administration the mean metabolite:parent AUC ratio was less than 10% for both total topotecan and topotecan lactone. An O-glucuronide of topotecan and N-desmethyl topotecan has been identified in the urine.

*In vitro*, topotecan did not inhibit human cytochrome P450 enzymes CYP1A2, CYP2A6, CYP2C8/9, CYP2C19, CYP2D6, CYP2E, CYP3A, or CYP4A nor did it inhibit the human cytosolic enzymes dihydropyrimidine dehydrogenase or xanthine oxidase.

### **Elimination**

Following i.v. administration, the plasma concentrations decline bi-exponentially. The pharmacokinetics of i.v. topotecan are approximately dose proportional. There is little or no accumulation of topotecan with repeated daily dosing, and there is no evidence of a change in the pharmacokinetics with multiple dosing.

Following i.v. administration of topotecan at doses of 0.5 to 1.5 mg/m<sup>2</sup> as a 30 minute infusion daily for five days, topotecan demonstrated a high clearance (64 L/h), approximately 2/3 of liver blood flow.

Overall recovery of drug-related material following five daily doses of topotecan was 71 to 76% (i.v.) of the administered dose. Approximately 51% was excreted as total topotecan and 2.5% was excreted as N-desmethyl topotecan in the urine. Faecal elimination of total topotecan accounted for 18% of the administered dose while faecal elimination of N-desmethyl topotecan was approximately 1.5%. Overall, the N-desmethyl metabolite contributed a mean of less than 7% (range 4 to 9%) of the total drug-related material accounted for in the urine and faeces. The topotecan-O-glucuronide and N-desmethyl topotecan-O-glucuronide in the urine were less than or equal to 2% of the dose.

When given in combination with cisplatin (cisplatin day 1, topotecan days 1 to 5), the clearance of topotecan was reduced on day 5 compared to day 1 (19.1 L/h/m<sup>2</sup> compared to 21.3 L/h/m<sup>2</sup>) (see section INTERACTIONS). In population studies, the co-administration of granisetron, ondansetron, morphine or corticosteroids did not appear to have a significant effect on the pharmacokinetics of topotecan.

### **Special Patient Populations**

In a population study with i.v. topotecan, a number of factors including age, weight and ascites had no significant effect on clearance (see section INTERACTIONS).

### **Pediatric patients (below 18 years)**

The pharmacokinetics of topotecan in paediatrics was studied in paediatrics who had either received a 24 hour continuous infusion of between 2 and 7.5 mg/m<sup>2</sup> or a 72 hour continuous infusion of between 0.75 and 1.95 mg/m<sup>2</sup>/day. In both studies the clearance was similar to that found in adults using the same dosing regimens.

### **Renal impairment**

Plasma clearance of i.v. topotecan in patients with renal impairment (creatinine clearance 40 to 60 ml/min.) decreased to about 67% compared with control patients. Volume of distribution was slightly decreased and thus half-life only increased by 14%. In patients with moderate renal impairment (creatinine clearance 20 to 39 ml/min) topotecan plasma clearance was reduced to 34% of the value in control patients. Volume of distribution also decreased by about 25% which resulted in an increase in mean half-life from 1.9 hours to 4.9 hours.

### **Hepatic impairment**

Plasma clearance of topotecan lactone after i.v. administration in patients with hepatic impairment (serum bilirubin in the range 1.5 to 10 mg/dL) decreased to about 67% when compared with a control group of patients. Topotecan half-life was increased by about 30% but no clear change in volume of distribution was observed. Total topotecan plasma clearance in patients with hepatic impairment only decreased by about 10% compared with the control group of patients.

## **CLINICAL STUDIES**

### **Small Cell Lung Carcinoma**

In a comparative study (SK&F 104864/090) of i.v. topotecan and the treatment regimen CAV (cyclophosphamide, doxorubicin, vincristine) in relapsed small cell lung carcinoma which was sensitive to first line therapy, there was a numerically superior response rate with topotecan 22%

(95% CI; 15, 30) versus CAV 15% (95% CI; 8, 22). All radiological responses were independently verified. "Sensitivity" was defined as 3 months treatment-free interval; to facilitate recruitment this was amended to 60 days treatment-free interval. The median duration of response (14 weeks for topotecan and 15 weeks for CAV), time to progression (topotecan 13 weeks versus CAV 12 weeks) and survival time (topotecan 25 weeks versus CAV 22 weeks) were similar for both treatments. Using the Patient Symptom Assessment in Lung Cancer Scale, patients treated with topotecan reported greater symptom relief improvement over CAV for the following symptoms: dyspnea, cough, chest pain, loss of appetite, interference with sleep, hoarseness, fatigue and interference with daily activities, with significant results for dyspnea, hoarseness, fatigue and interference with daily activities.

Hemoptysis was alleviated to a greater (but not statistically significant) extent in patients treated with CAV. The time to worsening of the following symptoms was numerically greater (i.e. delayed worsening) for topotecan treated patients than for CAV: dyspnea, loss of appetite, interference with sleep, cough, interference with daily activity, hoarseness and fatigue, with significant results for dyspnea and loss of appetite. Time to worsening for chest pain was similar for i.v. topotecan and CAV treatments, and for hemoptysis numerically greater for CAV (30th May 1997 cut-off).

Efficacy data for study SKF104864/090 was updated based on a second clinical cut-off of the 20th March 1998. Qualitatively the efficacy data remained unchanged with only minor numerical updates for response rate, topotecan 24.3% versus CAV 18.3% and median survival, topotecan 25 weeks versus CAV 24.77 weeks.

### **Ovarian carcinoma**

In a comparative study (SK&F 104864/039) of i.v. topotecan (n=112) and i.v. paclitaxel (n=114) in relapsed ovarian carcinoma, there was a numerically superior response rate with topotecan 20.5% (95% CI; 13.1 to 28.0) versus paclitaxel 14% (95% CI; 7.7 to 20.4). The difference between treatments was 6.5% (95% CI -3.3, 16.3). All radiological responses were independently verified. The median duration of response (25.9 weeks for topotecan and 21.6 weeks for paclitaxel), median time to progression (topotecan 18.9 weeks (95% CI 12.1, 23.6) versus paclitaxel 14.7 weeks (95% CI 11.9, 18.3)) and median survival (topotecan 63.0 weeks (95% CI 46.6, 71.9) versus paclitaxel 53 weeks (95% CI 42.3, 68.7)).

**Note:** All data denote values for ITT analysis population.

### **Cervical carcinoma**

In a randomized, comparative phase III trial conducted by the Gynaecological Oncology Group (GOG 0179), topotecan plus cisplatin (n=147) was compared with cisplatin alone (n=146) for the treatment of confirmed Stage IV-B, recurrent or persistent carcinoma of the cervix where curative treatment with surgery and/or radiation was not considered appropriate. No patient had received primary chemotherapy with cisplatin or any other cytotoxic agent. The overall response rate in the topotecan plus cisplatin group of 24% was significantly higher ( $p=0.0073$ ) than the 12% achieved in the cisplatin alone group. The complete response rate in the topotecan plus cisplatin and cisplatin alone arms were 10% and 3% respectively. This was associated with a longer progression-free survival of 4.6 (range 3.5 to 5.7) months versus 2.9 (range 2.6 to 3.5) months ( $p=0.026$ ) and a longer overall survival of 9.4 (range 7.9 to 11.9) months compared to 6.5 (range 5.8 to 8.8) months ( $p=0.033$ ) in the topotecan plus cisplatin arm compared to the cisplatin alone arm. The one year survival rate in the topotecan plus cisplatin group was 40.4% (95% CI; 32.3, 48.5) compared to 28% (95% CI; 20.6, 35.4) in the cisplatin alone group. Two year survival was 11.9 % (95% CI; 5.5, 18.3) and 7.1% (95% CI; 2.0, 12.2) for the two patient populations respectively. The secondary endpoint of health-related quality of life (HrQoL) was assessed using the Functional Assessment of Cancer Therapy-Cervix Cancer, Brief Pain Inventory as well as the UNISCALE. HrQoL assessments were made prior to randomization, prior to cycles 2 and 5 of treatment and nine months post-randomisation. Compared to cisplatin alone, the increased hematological toxicity seen with the combination of topotecan and cisplatin did not significantly reduce the patient HrQoL outcomes.

### **Integrated safety data**

Safety data is presented on an integrated data set of 631 patients with relapsed lung cancer and 523 patients with relapsed ovarian cancer administered 5583 courses of topotecan (see section ADVERSE DRUG REACTIONS).

## **Hematological**

**Neutropenia:** Severe (neutrophil count less than  $0.5 \times 10^9/L$ ) during course 1 was seen in 55% of the patients and with duration greater than or equal to 7 days in 21% and overall in 76% of patients (39% of courses). In association with severe neutropenia, fever or infection occurred in 11% of patients during course 1 and overall in 18% of patients (5% of courses). Median time to onset of severe neutropenia was nine days and the median duration was seven days. Severe neutropenia lasted beyond seven days in 11% of courses overall. Among all patients treated in clinical trials (including both those with severe neutropenia and those who did not develop severe neutropenia), 11% (4% of courses) developed fever and 26% (9% of courses) developed infection. In addition, 5% of all patients treated (1% of courses) developed sepsis.

**Thrombocytopenia:** Severe (platelets less than  $25 \times 10^9/L$  (as defined by v1 of CTC criteria)) in 25% of patients (8% of courses); moderate (platelets between  $25.0$  and  $50.0 \times 10^9/L$ ) in 25 % of patients (15% of courses). Median time to onset of severe thrombocytopenia was Day 15 and the median duration was 5 days. Platelet transfusions were given in 4% of courses. Reports of significant sequelae associated with thrombocytopenia including fatalities due to tumor bleeds have been infrequent.

**Anemia:** Moderate to severe (Hb less than 8.0 g/dl) in 37% of patients (14% of courses). Red cell transfusions were given in 52% of patients (21% of courses).

## **Non-hematological**

Frequently reported non-hematological effects were gastrointestinal such as nausea (52%), vomiting (32%), and diarrhea (19%), constipation (9%) and stomatitis (15%). Severe (grade 3 or 4) nausea, vomiting, diarrhea and stomatitis incidence was 4, 3, 2 and 1% respectively. Mild abdominal pain was also reported amongst 4% of patients.

Fatigue was observed in approximately 25% and asthenia in 16% of patients whilst receiving topotecan. Severe (grade 3 or 4) fatigue and asthenia incidence was 3% and 3% respectively.

Total or pronounced alopecia was observed in 30% of patients and partial alopecia in 15% of patients.

Other events occurring in patients that were recorded as related or possibly related to topotecan treatment were anorexia (13%), malaise (4%) and hyperbilirubinemia (1%).

Hypersensitivity reactions including rash, urticaria, angioedema and anaphylactic reactions have been reported rarely. In clinical trials, rash was reported in 4% of patients and pruritus in 1.5% of patients.

## **NON-CLINICAL SAFETY DATA**

### **Carcinogenicity and mutagenicity**

The carcinogenic potential of topotecan has not been studied. In common with a number of other cytotoxic agents, and resulting from its mechanism of action, topotecan is genotoxic to mammalian cells (mouse lymphoma cells and human lymphocytes) *in vitro* and mouse bone marrow cells *in vivo*.

### **Reproductive toxicology**

In reproductive toxicity studies with topotecan in rats, there was no effect on male or female fertility; however, in females rats super-ovulation and slightly increased pre-implantation loss were observed (see section FEMALES AND MALES OF REPRODUCTIVE POTENTIAL FOR REPRODUCTIVE TOXICITY).

## **INCOMPATIBILITIES**

None known.

## **STORAGE**

See folding box.

### **Shelf-Life**

The expiry date is indicated on the packaging.

Three years at temperatures up to 30°C. The vial must be protected from light and retained in its carton.

### **Reconstituted solutions**

It is recommended that the product is used immediately after reconstitution or stored in a refrigerator (2 to 8°C) and discarded after 24 hours, as the product contains no antibacterial preservative.

### **Diluted solutions**

It is recommended that diluted solutions are infused within 24 hours.

Hycamtin should not be used after the date marked "EXPIRY" on the pack.

Hycamtin must be kept out of the reach and sight of children.

## **INSTRUCTIONS FOR USE AND HANDLING**

**Precautions:** Hycamtin is a cytotoxic anti-cancer drug. As with other potentially toxic compounds, Hycamtin should be prepared under a vertical laminar flow hood while wearing gloves and protective clothing. If Hycamtin solution contacts the skin, wash the skin immediately and thoroughly with soap and water. If Hycamtin contacts mucous membranes, flush thoroughly with water.

Hycamtin must be reconstituted and further diluted before use.

Hycamtin 1 mg vials must be reconstituted with 1.1 mL Sterile Water for Injection. Hycamtin 4 mg vials must be reconstituted with 4 mL Sterile Water for Injection. The reconstituted solutions provide 1 mg per mL of Hycamtin. Further dilution of the appropriate volume of the reconstituted solution with either 0.9% Sodium Chloride BP i.v. Infusion or 5% Dextrose BP i.v. Infusion is required to achieve a final concentration of between 25 and 50 micrograms/mL.

The normal procedures for proper handling and disposal of anti-cancer drugs should be adopted, including:

- Personnel should be trained to reconstitute the drug.
- Pregnant staff should be excluded from working with this drug.
- Personnel handling this drug during reconstitution should wear protective clothing including mask, goggles and gloves.
- All items for administration or cleaning, including gloves, should be placed in high-risk, waste disposal bags for high-temperature incineration. Liquid waste may be flushed with large amounts of water.
- Accidental contact with the skin or eyes should be treated immediately with copious amounts of water.

### **Manufacturer:**

See folding box.

## **A product of Novartis Pharma AG, Basel, Switzerland**

Further information is available from:

### **Novartis Healthcare Private Limited**

Gala No. 1-A & 2-A, Bldg. No. 28, Arihant Compound, Kopar, Purna, Tal - Bhiwandi,  
Dist - Thane - 421 302, India.

Information issued: India pack insert dtd 14 Nov 18 based on International Package leaflet (IPL) dated 10 Sep 18.

® = Registered Trademark of Novartis AG, Basel, Switzerland

## Trametinib 0.5 mg and 2 mg tablets

### MEQSEL®

Protein kinase inhibitor

## DESCRIPTION AND COMPOSITION

### Pharmaceutical form(s)

Trametinib 0.5 mg film-coated tablets— yellow, modified oval, biconvex, film-coated tablets with 'GS' debossed on one face and 'TFC' on the opposing face.

Trametinib 2 mg film-coated tablets— pink, round, biconvex, film-coated tablets with 'GS' debossed on one face and 'HMJ' on the opposing face.

Certain dosage strengths and dosage forms may not be available in all countries.

### Active substance

#### 0.5 mg film-coated tablets

Each film-coated tablet contains trametinib-dimethylsulfoxide (1:1) equivalent to 0.5 mg trametinib

**2 mg film-coated tablets** - Each film-coated tablet contains trametinib-dimethylsulfoxide (1:1) equivalent to 2 mg trametinib

### Excipients

#### Tablet core:

Mannitol

Microcrystalline cellulose

Hypromellose

Croscarmellose sodium

Magnesium stearate (vegetable source)

Sodium laurylsulfate

Colloidal silicon dioxide

#### Tablet film-coating

Hypromellose

Titanium dioxide

Polyethylene glycol

Iron oxide yellow (for 0.5 mg tablets)

Polysorbate 80 and Iron oxide red (for 2 mg tablets).

Pharmaceutical formulations may vary between countries.

## **INDICATIONS**

### **Unresectable or metastatic melanoma**

Meqsel in combination with dabrafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see CLINICAL STUDIES).

Meqsel as a monotherapy is indicated for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation (see CLINICAL STUDIES).

Meqsel as monotherapy has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy (see CLINICAL STUDIES).

### **Advanced non-small cell lung cancer**

Meqsel in combination with dabrafenib is indicated for the treatment of patients with advanced non-small cell lung cancer (NSCLC) with a BRAF V600 mutation.

## **DOSAGE REGIMEN AND ADMINISTRATION**

Treatment with Meqsel should be initiated by a physician experienced in the use of anticancer therapies.

### **Dose regimen**

#### **General target population**

#### **Adults**

Confirmation of BRAF V600 mutation using an approved/validated test is required for selection of patients appropriate for treatment with Meqsel as monotherapy and in combination with dabrafenib (see CLINICAL STUDIES).

When Meqsel is used in combination with dabrafenib, please refer to the full dabrafenib prescribing information (see DOSAGE REGIMEN AND ADMINISTRATION).

The recommended dose of Meqsel either as monotherapy or in combination with dabrafenib is 2 mg given orally once daily with a full glass of water.

Meqsel should be taken without food, at least one hour before or two hours after a meal (see CLINICAL PHARMACOLOGY).

When Meqsel and dabrafenib are taken in combination, the once-daily dose of Meqsel should be taken at the same time each day with either the morning dose or the evening dose of dabrafenib.

If a dose of Meqsel is missed, it should only be taken if it is more than 12 hours until the next scheduled dose.

### **Dose adjustments**

#### **Meqsel as Monotherapy and in combination with dabrafenib**

The management of adverse events/adverse drug reactions may require treatment interruption, dose reduction, or treatment discontinuation (see Table 1 and Table 2).

**Table 1 Recommended Meqsel dose level reductions**

Dose Level	Meqsel Dose
Starting dose	2 mg once daily
First dose reduction	1.5 mg once daily
Second dose reduction	1 mg once daily

Dose adjustment for Meqsel,, below 1 mg once daily is not recommended, whether used as monotherapy or in combination with Rafinlar.

**Table 2: Meqsel dose modification schedule**

Grade (CTC-AE)*	Dose Modifications
Grade 1 or Grade 2 (Tolerable)	Continue treatment and monitor as clinically indicated.
Grade 2 (Intolerable) or Grade 3	Interrupt therapy until toxicity is grade 0 to 1 and reduce by one dose level when resuming therapy.
Grade 4	Discontinue permanently, or interrupt therapy until Grade 0 to 1 and reduce by one dose level when resuming therapy.

\* The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)

When an individual's adverse reactions are under effective management, dose re-escalation following the same dosing steps as de-escalation may be considered. The Meqsel dose should not exceed 2 mg once daily.

If treatment related toxicities occur when Meqsel is used in combination with dabrafenib then both treatments should be simultaneously dose reduced, interrupted or discontinued with the exceptions shown below.

Exceptions where dose modifications are necessary for Meqsel only:

- Left ventricular ejection fraction (LVEF) reduction
- Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED)
- Pneumonitis and Interstitial Lung Disease (ILD)

**LVEF Reduction/Left Ventricular Dysfunction management:** Meqsel should be interrupted in patients who have an asymptomatic, absolute decrease of > 10 % in LVEF compared to baseline and the ejection fraction below the institution's lower limit of normal (LLN) (see WARNINGS AND PRECAUTIONS). If Meqsel is being used in combination with dabrafenib then therapy with dabrafenib may be continued at the same dose. If the LVEF recovers, treatment with Meqsel may be restarted, but the dose should be reduced by one dose level with careful monitoring. Meqsel should be permanently discontinued with Grade 3 or 4 left ventricular cardiac dysfunction or if repeatedly reduced LVEF does not recover.

**Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED) management:**

If RPED is diagnosed, the dose modification schedule (intolerable) in Table 2 above for Meqsel should be followed and, if Meqsel is being used in combination with dabrafenib, dabrafenib should be continued at the same dose. In patients who experience RVO, treatment with Meqsel should be permanently discontinued (see WARNINGS AND PRECAUTIONS).

**Pneumonitis and Interstitial Lung Disease (ILD) management:** For events of pneumonitis, follow dose modification guidelines in Table 2 for Meqsel only; no modification of dabrafenib is required when taken in combination with Meqsel.

Refer to the full prescribing information of dabrafenib for dose modification guidelines (see DOSAGE REGIMEN AND ADMINISTRATION).

## Special populations

### Renal impairment

No dosage adjustment is required in patients with mild or moderate renal impairment. Mild or moderate renal impairment had no significant effect on the population pharmacokinetics of Meqsel (see CLINICAL PHARMACOLOGY, Pharmacokinetics). There are no clinical data in patients with severe renal impairment; therefore, the potential need for starting dose adjustment cannot be determined. Meqsel should be used with caution in patients with severe renal impairment.

### Hepatic impairment

No dosage adjustment is required in patients with mild hepatic impairment. In a population pharmacokinetic analysis, Meqsel oral clearance and thus exposure was not significantly different in patients with mild hepatic impairment compared to patients with normal hepatic function (see CLINICAL PHARMACOLOGY, PHARMACOKINETICS). There are no clinical data in patients with moderate or severe hepatic impairment; therefore, the potential need for starting dose adjustment cannot be determined. Meqsel should be used with caution in patients with moderate or severe hepatic impairment.

### Pediatric patients (below 18 years)

The safety and efficacy of Meqsel in pediatric patients have not been established. Meqsel is not recommended in this age group.

### Geriatric patients (65 years or above)

No dosage adjustment is required in patients over 65 years of age (see CLINICAL PHARMACOLOGY PHARMACOKINETICS).

## CONTRAINDICATIONS

None.

## **WARNINGS AND PRECAUTIONS**

When Meqsel is used together with dabrafenib read the full prescribing information for dabrafenib section WARNINGS AND PRECAUTIONS.

### **LVEF Reduction/Left Ventricular Dysfunction:**

Meqsel has been reported to decrease LVEF (see ADVERSE DRUG REACTIONS). In clinical trials, the median time to onset of the first occurrence of left ventricular dysfunction, cardiac failure and LVEF decrease in patients treated with Meqsel as monotherapy or in combination with dabrafenib was between two to five months. Meqsel should be used with caution in patients with conditions that could impair left ventricular function. LVEF should be evaluated in all patients prior to initiation of treatment with Meqsel with a recommendation of periodic follow-up within eight weeks of initiating therapy, as clinically appropriate. LVEF should continue to be evaluated during treatment with Meqsel as clinically appropriate (see DOSAGE REGIMEN AND ADMINISTRATION).

### **Haemorrhage:**

Haemorrhagic events, including major hemorrhagic events have occurred in patients taking Meqsel as monotherapy and in combination with dabrafenib (see ADVERSE DRUG REACTIONS). Out of the 559 unresectable or metastatic melanoma patients treated with Meqsel in combination with dabrafenib, there were six fatal intracranial hemorrhagic cases (1%). Three cases were from study MEK115306 (COMBI-d) and three cases were from study MEK116513 (COMBI-v). Two out of 93 patients (2%) receiving Meqsel in combination with dabrafenib in a Phase II NSCLC trial had fatal intracranial hemorrhagic events. If patients develop symptoms of haemorrhage they should immediately seek medical care.

### **Visual Impairment:**

Disorders associated with visual disturbances, including chorioretinopathy or retinal pigment epithelial detachment (RPED) and Retinal Vein Occlusion (RVO) have been observed with Meqsel. Symptoms such as blurred vision, decreased acuity, and other visual phenomena have been reported in the clinical trials with Meqsel (see ADVERSE DRUG REACTIONS). Meqsel is not recommended in patients with a history of RVO. A thorough ophthalmological evaluation should be performed at baseline and during treatment with Meqsel, if clinically warranted. If patients report visual disturbances at any time while on Meqsel therapy, additional ophthalmological evaluation should be undertaken. If a retinal abnormality is noted, treatment with Meqsel should be interrupted immediately and referral to a retinal specialist should be considered. If RPED is diagnosed, the dose modification schedule (intolerable) in Table 2 should be followed (see DOSAGE REGIMEN AND ADMINISTRATION). In patients who experience RVO, treatment with Meqsel should be permanently discontinued.

### **Rash:**

In clinical studies, rash has been observed in about 60 % of patients receiving Meqsel as monotherapy and 20 to 30% receiving Meqsel in combination with dabrafenib (see ADVERSE DRUG REACTIONS). The majority of these cases were Grade 1 or 2 and did not require any dose interruptions or dose reductions.

### **Deep vein thrombosis (DVT)/Pulmonary embolism (PE):**

DVT and PE can occur on Meqsel monotherapy and when Meqsel is used in combination with dabrafenib. Patients should be advised to immediately seek medical care if they develop symptoms of pulmonary embolism or deep vein thrombosis.

### **Pyrexia:**

Pyrexia was reported in the clinical trials with Meqsel. The incidence and severity of pyrexia are increased when Meqsel is used in combination with dabrafenib (see ADVERSE DRUG REACTIONS). In patients with unresectable or metastatic melanoma who received the combination dose of Meqsel 2 mg once daily and Rafinlar 150 mg twice daily developed pyrexia, approximately half of the first occurrences of pyrexia happened within the first month of therapy. About one-third of the patients receiving combination therapy who experienced pyrexia had three or more events. Pyrexia may be accompanied by severe rigors, dehydration, and hypotension which in some cases can lead to acute renal insufficiency. Serum creatinine and other evidence of renal function should be monitored during and following severe events of pyrexia. Serious non-infectious febrile events have been observed. These events responded well to dose interruption and/or dose reduction and supportive care in clinical trials.

For management of pyrexia see the full prescribing information for dabrafenib (see DOSAGE REGIMEN AND ADMINISTRATION, Dose adjustments).

### **Colitis and gastrointestinal perforation**

Colitis and gastrointestinal perforation, including fatal outcome, have been reported in patients taking Meqsel as monotherapy and in combination with dabrafenib (ADVERSE DRUG REACTIONS). Treatment with Meqsel monotherapy or in combination with dabrafenib should be used with caution in patients with risk factors for gastrointestinal perforation, including a history of diverticulitis, metastases to the gastrointestinal tract and concomitant use of medications with a recognized risk of gastrointestinal perforation.

If patients develop symptoms of colitis and gastrointestinal perforation they should immediately seek medical care.

## **ADVERSE DRUG REACTIONS**

### **Summary of the safety profile**

#### **Unresectable or metastatic melanoma**

##### **Meqsel monotherapy**

The safety of Meqsel monotherapy was evaluated in an integrated population of 329 patients with BRAF V600 mutant unresectable or metastatic melanoma treated with Meqsel 2 mg orally once daily in studies MEK114267, MEK113583, and MEK111054.. Of these patients, 211 patients were treated with Meqsel for BRAF V600 mutant melanoma in the randomized open-label study MEK114267 (see CLINICAL STUDIES). The most common adverse events ( $\geq 20\%$ ) for Meqsel were rash, diarrhoea, fatigue, oedema peripheral, nausea, and dermatitis acneiform. In clinical

trials with Meqsel, adverse events of diarrhoea and rash were managed with appropriate supportive care (see DOSAGE REGIMEN AND ADMINISTRATION).

*Meqsel and Rafinlar combination therapy:*

The safety of Meqsel and Rafinlar combination therapy was evaluated in two randomized Phase III studies of patients with BRAF V600 mutant unresectable or metastatic melanoma treated with Meqsel 2 mg orally once daily and Rafinlar 150 mg orally twice daily (see CLINICAL STUDIES). The most common adverse events ( $\geq 20\%$ ) for Meqsel and Rafinlar combination therapy were pyrexia, fatigue, nausea, headache, chills, diarrhoea, rash, arthralgia, hypertension, vomiting, peripheral oedema and cough.

*Tabulated summary of adverse events from clinical trials in metastatic melanoma:*

Adverse events from clinical trials in patients with unresectable or metastatic melanoma are listed by MedDRA system organ class in Table 3 and Table 4 for Meqsel monotherapy and Meqsel in combination with Rafinlar, respectively. Within each system organ class, the adverse events are ranked by frequency, with the most frequent adverse events first. In addition, the corresponding frequency category for each adverse event is based on the following convention (CIOMS III): very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

**Table 3 Unresectable or metastatic melanoma-adverse events for Meqsel monotherapy**

Adverse events	Frequency category Integrated Safety Data N=329
<b>Infections and Infestations</b>	
Folliculitis	Common
Paronychia	Common
Cellulitis	Common
Rash pustular	Common
<b>Blood and lymphatic system disorders</b>	
Anaemia	Common
<b>Immune system disorders</b>	
Hypersensitivity <sup>1)</sup>	Common
<b>Metabolism and nutrition disorders</b>	
Dehydration	Common
<b>Eye disorders</b>	
Vision blurred	Common
Periorbital oedema	Common
Visual Impairment	Common

Chorioretinopathy	Uncommon
Retinal vein occlusion	Uncommon
Papilloedema	Uncommon
Retinal detachment	Uncommon
<b>Cardiac disorders</b>	
Left ventricular dysfunction	Common
Ejection fraction decreased	Common
Bradycardia	Common
Cardiac failure	Uncommon
<b>Vascular disorders</b>	
Hypertension	Very common
Haemorrhage <sup>2)</sup>	Very common
Lymphoedema	Common
<b>Respiratory, thoracic and mediastinal disorders</b>	
Cough	Very common
Dyspnea	Very common
Epistaxis	Common
Pneumonitis	Common
Interstitial lung disease	Uncommon
<b>Gastrointestinal disorders</b>	
Diarrhoea	Very common
Nausea	Very Common
Vomiting	Very Common
Constipation	Very Common
Abdominal pain	Very Common
Dry mouth	Very Common
Stomatitis	Common
Gastrointestinal perforation	Uncommon
Collitis	Uncommon
<b>Skin and Subcutaneous Tissue Disorders</b>	
Rash	Very common
Dermatitis acneiform	Very common
Dry Skin	Very common
Pruritus	Very common
Alopecia	Very common
Skin chapped	Common
Erythema	Common
Palmar-plantar erythrodysaesthesia syndrome	Common
Skin fissures	Common
<b>Musculoskeletal and connective tissue disorder</b>	
Rhabdomyolysis	Uncommon

Blood creatine phosphokinase increased	Common
<b>General disorders</b>	
Fatigue	Very common
Oedema peripheral	Very common
Pyrexia	Very common
Face oedema	Common
Mucosal inflammation	Common
Asthenia	Common
<b>Investigations</b>	
Aspartate aminotransferase increased	Common
Alanine aminotransferase increased	Common
Blood alkaline phosphatase increased	Common
1) May present with symptoms such as fever, rash, increased liver function tests, and visual disturbances. 2) The majority of bleeding events were mild. Major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages have been reported.	

Table 4 lists adverse events when Meqsel was used in combination with Rafinlar from the randomized double-blind Phase III study MEK115306 (N=209), and integrated safety data from MEK115306 (N=209) and from the randomized open-label Phase III study MEK116513 (N=350).

**Table 4: Unresectable or metastatic Melanoma -Adverse events for Meqsel in combination with Rafinlar**

Adverse events	Frequency category	
	MEK115306 (COMBI-d) N=209	MEK115306 (COMBI-d) plus MEK116513 (COMBI-v) Integrated Safety Data N=559
<b>Infections and Infestations</b>		
Urinary tract infection	Very common	Common
Nasopharyngitis	Very common	Very common
Cellulitis	Common	Common
Folliculitis	Common	Common
Paronychia	Common	Common
Rash pustular	Common	Common
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>		
Cutaneous squamous cell carcinoma (SCC) including SCC of the skin, SCC in situ (Bowen's disease) and keratoacanthoma	Common	Common
Papilloma including skin papilloma	Common	Common
Seborrhoeic keratosis	Common	Common

Adverse events	Frequency category	
	MEK115306 (COMBI-d) N=209	MEK115306 (COMBI-d) plus MEK116513 (COMBI-v) <b>Integrated Safety Data</b> <b>N=559</b>
Acrochordon (skin tags)	Common	Uncommon
New primary melanoma	Uncommon	Uncommon
<b>Blood and lymphatic system disorders</b>		
Neutropenia	Very common	Common
Anaemia	Common	Common
Thrombocytopenia	Common	Common
Leukopenia	Common	Common
<b>Immune system disorders</b>		
Hypersensitivity	Uncommon	Uncommon
<b>Metabolic and nutrition disorders</b>		
Decreased appetite	Very common	Very common
Dehydration	Common	Common
Hyperglycaemia	Common	Common
Hyponatraemia	Common	Common
Hypophosphataemia	Common	Common
<b>Nervous system disorders</b>		
Headache	Very common	Very common
Dizziness	Very common	Very common
<b>Eye disorders</b>		
Vision blurred	Common	Common
Visual impairment	Common	Common
Chorioretinopathy	Uncommon	Uncommon
Uveitis	Uncommon	Uncommon
Retinal detachment	Uncommon	Uncommon
Periorbital oedema	Uncommon	Uncommon
<b>Cardiac disorders</b>		
Ejection fraction decreased	Common	Common
Bradycardia	Common	Common
Left ventricular dysfunction	Not reported	Uncommon
Cardiac failure	Not reported	Uncommon
<b>Vascular disorders</b>		
Hypertension	Very common	Very common
Haemorrhage <sup>1)</sup>	Very common	Very common
Hypotension	Common	Common
Lymphoedema	Uncommon	Common
<b>Respiratory, thoracic and mediastinal disorders</b>		
Cough	Very common	Very common

Adverse events	Frequency category	
	MEK115306 (COMBI-d) N=209	MEK115306 (COMBI-d) plus MEK116513 (COMBI-v) Integrated Safety Data N=559
Dyspnoea	Common	Common
Pneumonitis	Uncommon	Uncommon
Interstitial lung disease	Not reported	Uncommon
<b>Gastrointestinal disorders</b>		
Abdominal pain	Very common	Very common
Constipation	Very common	Very common
Diarrhoea	Very common	Very common
Nausea	Very common	Very common
Vomiting	Very common	Very common
Dry mouth	Common	Common
Stomatitis	Common	Common
Pancreatitis	Uncommon	Uncommon
Gastrointestinal perforation	Not reported	Uncommon
Colitis	Uncommon	Uncommon
<b>Skin and subcutaneous tissue disorders</b>		
Dry skin	Very common	Very common
Pruritus	Very common	Very common
Rash	Very common	Very common
Dermatitis acneiform	Very common	Common
Erythema	Common	Common
Actinic keratosis	Common	Common
Night sweats	Common	Common
Hyperkeratosis	Common	Common
Alopecia	Common	Common
Palmar-plantar erythrodysesthesia syndrome	Common	Common
Skin lesion	Common	Common
Hyperhidrosis	Common	Common
Skin fissures	Common	Common
Panniculitis	Common	Common
Photosensitivity <sup>2)</sup>	Common	Common
<b>Musculoskeletal and connective tissue disorders</b>		
Arthralgia	Very common	Very common
Myalgia	Very common	Very common
Pain in extremity	Very common	Very common
Muscle spasms	Common	Common
Blood creatine phosphokinase increased	Common	Common
Rhabdomyolysis	Not reported	Uncommon

Adverse events	Frequency category	
	MEK115306 (COMBI-d) N=209	MEK115306 (COMBI-d) plus MEK116513 (COMBI-v) Integrated Safety Data N=559
<b>Renal disorders</b>		
Renal failure	Uncommon	Common
Nephritis	Uncommon	Uncommon
Renal failure acute	Not reported	Uncommon
<b>General disorders and administration site disorders</b>		
Fatigue	Very common	Very common
Oedema peripheral	Very common	Very common
Pyrexia	Very common	Very common
Chills	Very common	Very common
Asthenia	Very common	Very common
Mucosal inflammation	Common	Common
Influenza-like illness	Common	Common
Face oedema	Common	Common
<b>Investigations</b>		
Alanine aminotransferase increased	Very common	Very common
Aspartate aminotransferase increased	Very common	Very common
Blood alkaline phosphatase increased	Common	Common
Gamma-glutamyltransferase increased	Common	Common
<p>1) <i>The majority of bleeding events were mild. Major events, defined as symptomatic bleeding in a critical area or organ, and fatal intracranial haemorrhages have been reported.</i></p> <p>2) <i>Photosensitivity cases were also observed in post-marketing experience. All cases reported in the COMBI-d and COMBI-v were Grade – 1 and no dose modification was required</i></p>		

### Metastatic melanoma patients with brain metastases

The safety profile observed in study BRF117277/DRB436B2204 (COMBI-MB) in metastatic melanoma patients with brain metastases is consistent with the safety profile of Meqsel in combination with Rafinlar in unresectable or metastatic melanoma (see CLINICAL STUDIES).

### Advanced non-small cell lung cancer (NSCLC)

*Meqsel in combination with Rafinlar:*

The safety of Meqsel in combination with Rafinlar was evaluated in a Phase II, multicenter, multi-cohort, non-randomized, open label study of patients with BRAF V600E mutation positive metastatic NSCLC (see CLINICAL STUDIES).

In the Meqsel 2 mg orally once daily and Rafinlar 150 mg orally twice daily arms (Cohorts B and C) the most common adverse events ( $\geq 20\%$ ) reported for Meqsel and Rafinlar combination therapy were pyrexia, nausea, vomiting, peripheral oedema,

diarrhoea, decreased appetite, asthenia, dry skin, chills, cough, fatigue, rash and dyspnea.

Table 5 lists the adverse drug reactions for Meqsel in combination with Rafinlar occurring at an incidence  $\geq 10\%$  for all adverse drug reactions or at an incidence  $\geq 2\%$  for Grade 3 and Grade 4 adverse drug reactions or events which are medically significant in Cohorts B and C of study BRF113928.

Adverse drug reactions are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent adverse drug reactions first. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ).

**Table 5: Advanced NSCLC - Adverse drug reactions for Meqsel in combination with Rafinlar**

Adverse drug reaction	Meqsel in combination with Rafinlar N=93		
	All grades %	Grades 3/4 %	Frequency category
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>			
Cutaneous squamous cell carcinoma	3	2	Common
<b>Blood and lymphatic system disorders</b>			
Neutropenia <sup>1)</sup>	15	8	Very common
Leukopenia	6	2	Common
<b>Metabolism and nutrition disorders</b>			
Hyponatraemia	14	9	Very common
Dehydration	8	3	Common
<b>Eye disorders</b>			
Detachment of retina/retinal pigment epithelium	2	NR	Common
<b>Nervous system disorders</b>			
Headache	16	NR	Very common
Dizziness	14	NR	Very common
<b>Cardiac disorders</b>			
Ejection fraction decreased	9	4	Common
<b>Vascular disorders</b>			
Haemorrhage <sup>2)</sup>	26	3	Very common
Hypotension	15	2	Very common
Pulmonary embolism	4	2	Common

Adverse drug reaction	Meqsel in combination with Rafinlar N=93		
	All grades %	Grades 3/4 %	Frequency category
Hypertension	8	6	Common
<b>Gastrointestinal disorders</b>			
Nausea	46	NR	Very common
Vomiting	37	3	Very common
Diarrhoea	33	2	Very common
Decreased appetite	28	NR	Very common
Constipation	16	NR	Very common
Pancreatitis acute	1	NR	Common
<b>Skin and subcutaneous tissue disorders</b>			
Erythema	10	NR	Very common
Dry skin	32	1	Very common
Rash <sup>3)</sup>	31	3	Very common
Pruritus <sup>4)</sup>	15	2	Very common
Hyperkeratosis <sup>5)</sup>	13	1	Very common
<b>Musculoskeletal and connective tissue disorders</b>			
Muscle spasms	10	NR	Very common
Arthralgia	16	NR	Very common
Myalgia	13	NR	Very common
<b>Renal and urinary disorders</b>			
Renal failure	3	1	Common
Tubulointerstitial nephritis	2	2	Common
<b>General disorders and administration site disorders</b>			
Pyrexia	55	5	Very common
Asthenia <sup>6)</sup>	47	6	Very common
Oedema <sup>7)</sup>	35	NR	Very common
Chills	24	1	Very common
<b>Investigations</b>			
Blood alkaline phosphatase increased	12	NR	Very common
Aspartate aminotransferase increased	11	2	Very common
Alanine aminotransferase increased	10	4	Very common

<sup>1)</sup> Neutropenia includes neutropenia and neutrophil count decreased. Neutrophil count decreased qualified as a neutropenia event.

Adverse drug reaction	Meqsel in combination with Rafinlar N=93		
	All grades %	Grades 3/4 %	Frequency category
<sup>2)</sup> <i>Haemorrhage includes cases of haemoptysis, haematoma, epistaxis, purpura, haematuria, subarachnoid haemorrhage, gastric haemorrhage, urinary bladder haemorrhage, contusion, haematochezia, injection site haemorrhage, melaena, pulmonary and retroperitoneal haemorrhage.</i>			
<sup>3)</sup> <i>Rash includes rash, rash generalized, rash papular, rash macular, rash maculo-papular, and rash pustular.</i>			
<sup>4)</sup> <i>Pruritus includes pruritus, pruritus generalized, and eye pruritus.</i>			
<sup>5)</sup> <i>Hyperkeratosis includes hyperkeratosis, actinic keratosis, seborrhoeic keratosis, and keratosis pilaris.</i>			
<sup>6)</sup> <i>Asthenia also includes fatigue and malaise.</i>			
<sup>7)</sup> <i>Oedema includes generalized oedema and peripheral oedema.</i>			
NR: Not Reported			

## INTERACTIONS

### Monotherapy

As Trametinib is metabolized predominantly via deacetylation mediated by hydrolytic enzymes (including carboxylesterases), its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions. Trametinib repeat-dose exposure was not affected by co-administration with a cytochrome P450 (CYP) 3A4 inducer.

Based on *in vitro* and *in vivo* data, Meqsel is unlikely to significantly affect the pharmacokinetics of other medicinal products via interactions with CYP enzymes or transporters (see CLINICAL PHARMACOLOGY, Pharmacokinetics). Repeat dose administration of Meqsel 2 mg once daily had no clinically relevant effect on the single dose  $C_{max}$  and AUC of dabrafenib, a CYP2C8/CYP3A4 substrate.

### Combination therapy and non-fixed dose combination therapy

#### *Combination with Rafinlar*

Co-administration of repeat dosing of Meqsel 2 mg once daily and Rafinlar 150 mg twice daily resulted in a 16% increase in dabrafenib  $C_{max}$  and a 23% increase in dabrafenib AUC. A small decrease in Trametinib bioavailability, corresponding to a decrease in AUC of 12%, was estimated when Meqsel is administered in combination with Rafinlar using a population pharmacokinetic analysis. These changes in dabrafenib or trametinib  $C_{max}$  and AUC are considered not clinically relevant. See the full prescribing information for dabrafenib for guidelines on drug interactions associated with Rafinlar monotherapy.

## PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

### Pregnancy

#### Risk summary

Meqsel can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Meqsel in pregnant women. Reproductive

studies in animals (rats and rabbits) have demonstrated that trametinib induces maternal and developmental toxicity. In rats decreased fetal weight and increased incidences of post implantation loss were observed following maternal exposure to trametinib at concentrations 0.3 and 1.8 times the exposure in humans at the highest recommended dose of 2 mg once daily. In rabbits, decreased fetal weight and increased incidence of variations in ossification and post implantation loss were observed following maternal exposure to trametinib at concentrations 0.09 and 0.3 times the exposure in humans at the highest recommended dose of 2 mg once daily. Pregnant women should be advised of the potential risk to the fetus.

### **Animal data**

In embryo-fetal development studies, rats and rabbits received oral doses of trametinib up to 0.125 mg/kg/day and 0.31 mg/kg/day, respectively, during the period of organogenesis. In rats at  $\geq 0.031$  mg/kg/day and 0.125 mg/kg/day, maternal systemic exposures (AUC) were 110 ng\*h/mL and 684 ng\*h/mL, respectively, corresponding to approximately 0.3 and 1.8 times the exposure in humans at the highest recommended dose of 2 mg once daily. At doses  $\geq 0.031$  mg/kg/day developmental toxicity consisted of decreased fetal weights. At a dose of 0.125 mg/kg/day there was maternal toxicity and increases in post implantation loss. In rabbits at  $\geq 0.039$  mg/kg/day and 0.15 mg/kg/day, maternal systemic exposures (AUC) were 31.9 ng\*h/mL and 127 ng\*h/mL, respectively corresponding to approximately 0.09 and 0.3 times the exposures in humans at the highest recommended dose of 2 mg once daily. At doses  $\geq 0.039$  mg/kg/day developmental toxicity consisted in decreased fetal body weight and increased incidence of variations in ossification. At doses 0.15 mg/kg/day there were increases in post-implantation loss, including total loss of pregnancy, compared with control animals.

### **Lactation**

#### **Risk summary**

There are no data on the effect of Meqsel on the breast-fed child, or the effect of Meqsel on milk production. Because many drugs are transferred into human milk and because of the potential for adverse reactions in nursing infants from Meqsel, a nursing woman should be advised on the potential risks to the child. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for Meqsel and any potential adverse effects on the breast-fed child from Meqsel or from the underlying maternal condition.

### **Females and males of reproductive potential**

#### **Contraception**

##### **Females**

Females of reproductive potential should be advised that animal studies have been performed showing Meqsel to be harmful to the developing fetus. Sexually-active females of reproductive potential are recommended to use effective contraception (methods that result in less than 1% pregnancy rates) when taking Meqsel and for atleast 16 weeks after stopping treatment with Meqsel.

Females of reproductive potential receiving Meqsel in combination with dabrafenib should be advised that dabrafenib may decrease the efficacy of oral or any other systemic hormonal contraceptives and an effective alternative method of contraception should be used.

### ***Males***

Male patients (including those that have had a vasectomy) with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during sexual intercourse while taking Meqsel monotherapy or in combination with Rafinlar and for at least 16 weeks after stopping treatment with Meqsel.

### ***Infertility***

There is no information on the effect of Meqsel on human fertility. In animals, no fertility studies have been performed, but adverse effects were seen on female reproductive organs (see NON-CLINICAL SAFETY DATA). Meqsel may impair fertility in humans.

## **OVERDOSAGE**

No cases of overdose have been reported. There were no cases of Meqsel dose above 4 mg once daily reported from the clinical trials. Doses up to 4 mg orally once daily and loading doses of 10 mg orally once daily administered on two consecutive days, have been evaluated in clinical trials.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available. There is no specific treatment for an overdose of trametinib. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary. Hemodialysis is not expected to enhance the elimination as trametinib is highly bound to plasma proteins.

## **CLINICAL PHARMACOLOGY**

### **Mechanism of action (MOA)**

#### *Meqsel Monotherapy - Melanoma and NSCLC*

Trametinib (Meqsel) is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinases 1 (MEK1) and 2 (MEK2) activation and kinase activity. MEK proteins are critical components of the extracellular signal-regulated kinase (ERK) pathway. In melanoma and other cancers, this pathway is often activated by mutated forms of BRAF which activate MEK and stimulate tumour cell growth. Trametinib inhibits MEK kinaseactivity activity, suppresses growth of BRAF V600 mutant melanoma and non-small cell lung cancer (NSCLS) cell lines *in vitro* and demonstrates anti-tumour effects in BRAF V600 mutant melanoma xenograft models.

#### *Meqsel in combination with dabrafenib - Melanoma and NSCLC*

Dabrafenib is a potent, selective, ATP-competitive inhibitor of the BRAF (both wild-type and V600 variants) and wild type CRAF kinases. Oncogenic mutations in BRAF lead to constitutive activation of the RAS/RAF/MEK/ERK pathway and stimulation of tumor cell growth. Because, co-treatment with Meqsel and Rafinlar results in concomitant inhibition of two kinases in this pathway, BRAF and MEK, the combination provides

superior pathway suppression relative to either agent alone. The combination of trametinib with dabrafenib is synergistic/additive in BRAF V600 mutation positive melanoma and NSCLC cell lines *in vitro* and delays the emergence of resistance *in vivo* in BRAF V600 mutation positive melanoma xenografts.

### **Pharmacodynamics (PD)**

Trametinib suppressed levels of phosphorylated ERK in BRAF V600 mutant melanoma and NSCLC tumour cell lines and melanoma xenografts models.

In patients with BRAF and NRAS mutant melanoma, administration of Meqsel resulted in dose-dependent changes in tumor biomarkers including inhibition of phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation), and increases in p27 (a marker of apoptosis). The mean trametinib concentrations observed following repeat dose administration of 2 mg once daily exceeds the preclinical target concentration over the 24-hr dosing interval, thereby providing sustained inhibition of the MEK pathway.

### **Cardiac electrophysiology**

#### *Study MEK111054*

Initially the QT prolongation potential of trametinib was assessed as part of the first time in human study to determine the relationship between the independently manually-read QTc interval and plasma concentrations of trametinib using a nonlinear mixed effects model. Data were available in 50 patients with a total of 498 matched QTc values. Based on the concentration-QTc analysis, Meqsel showed no apparent potential to alter the QTc interval. At the mean  $C_{max}$  value observed at the recommended dose of 2 mg once daily, the median increase in QTc is 2.2 msec (90 % CI: 0.2, 4.0).

To confirm the lack of effect on QTc, the QT prolongation potential of Meqsel was further assessed in a dedicated, stand-alone Phase I study in 35 patients (32 patients completed the study) with solid tumors. Patients received 3 mg matched placebo on study day 1 followed by a 2 mg once daily dose of Meqsel and 2 tablets of 0.5 mg matched placebo on study days 2 to 14. On study day 15, all patients received a single dose of 3 mg Meqsel (supratherapeutic dose). The study showed no potential for Meqsel to alter the QTcF interval after repeat dose administration of 2 mg, including at the supratherapeutic dose of 3 mg on day 15. At a dose 1.5 times the maximum recommended dose, Meqsel does not prolong the QT interval to any clinically relevant extent.

### **Pharmacokinetics (PK)**

#### **Absorption**

Trametinib is absorbed orally with median time to achieve peak concentrations of 1.5 hours post-dose. The mean absolute bioavailability of a single 2 mg tablet dose is 72 % relative to an intravenous (IV) microdose. The increase in exposure ( $C_{max}$  and AUC) was dose-proportional following repeat dosing. Following administration of 2 mg daily, geometric mean  $C_{max}$ ,  $AUC(0-\tau)$  and pre dose concentration were 22.2 ng/ml, 370 ng\*hr/ml and 12.1 ng/ml, respectively with a low peak:trough ratio (1.8). Inter-subject variability was low (< 28 %). Administration of a single dose of trametinib with a high-

fat, high-calorie meal resulted in a 70 % and 10 % decrease in  $C_{max}$  and AUC, respectively compared to fasted conditions (see DOSAGE REGIMEN AND ADMINISTRATION).

## Distribution

Binding of trametinib to human plasma proteins is 97.4 %. Trametinib has a volume of distribution of 1,060 L determined following administration of a 5 microgram IV microdose.

## Biotransformation/Metabolism

*In vitro* and *in vivo* studies demonstrated that trametinib is metabolized predominantly via deacetylation alone or in combination with mono-oxygenation. The deacetylated metabolite was further metabolized by glucuronidation. The deacetylation is mediated by the carboxy-esterase 1b,1c and 2) and may also be mediated by other hydrolytic enzymes.

## Elimination

Trametinib accumulates with repeat daily dosing with a mean accumulation ratio of 6.0 following a 2 mg once daily dose. Mean terminal half-life is 127 hours (5.3 days) after single dose administration. Steady-state was achieved by Day 15. Trametinib plasma IV clearance is 3.21 l/hr.

Total dose recovery is low after a 10-day collection period (< 50 %) following administration of a single oral dose of radiolabelled trametinib as a solution, due to the long half-life. Drug-related material was excreted predominantly in the feces ( $\geq 81\%$  of recovered radioactivity) and to a small extent in urine ( $\leq 19\%$ ). Less than 0.1% of the excreted dose was recovered as parent in urine.

## *In Vitro* evaluation of drug interaction potential

### Effects of other drugs on trametinib:

*In vitro* and *in vivo* data suggest that the pharmacokinetics (PK) of trametinib is unlikely to be affected by other drugs. Trametinib is deacetylated via carboxylesterases and possibly other hydrolytic enzymes. There is little evidence from clinical studies for drug interactions mediated by carboxylesterases. CYP enzymes play a minor role in the elimination of trametinib and the compound is not a substrate of the following transporters: breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, OATP2B1, organic cation transporter (OCT) 1, multidrug resistance-associated protein (MRP) 2, and the multidrug and toxin extrusion protein (MATE) 1. Trametinib is an *in vitro* substrate of the efflux transporter P-glycoprotein (Pgp), but is unlikely to be significantly affected by inhibition of this transporter given its high passive permeability and high bioavailability.

## Special Populations

### Pediatric population (below 18 years)

No studies have been conducted to investigate the pharmacokinetics of Meqsel in paediatric patients.

#### **Geriatric population (65 years or above)**

Based on the population pharmacokinetics analysis, age had no relevant clinical effect on Meqsel pharmacokinetics.

#### **Gender/Weight**

Based on the population pharmacokinetic analysis, gender and weight were found to influence trametinib oral clearance. Although smaller female subjects are predicted to have higher exposure than heavier male subjects, these differences are unlikely to be clinically relevant and no dose adjustment is warranted.

#### **Race/Ethnicity**

There are insufficient data to evaluate the potential effect of race on trametinib pharmacokinetics.

#### **Renal Impairment**

Renal impairment is unlikely to have a clinically relevant effect on trametinib pharmacokinetics given the low renal excretion of trametinib. The pharmacokinetics of trametinib were characterized in 223 patients enrolled in clinical trials with trametinib who had mild renal impairment and 35 patients with moderate renal impairment using a population pharmacokinetic analysis. Mild and moderate renal impairment had no effect on trametinib exposure (< 6 % for either group). No data are available in patients with severe renal impairment (see DOSAGE REGIMEN AND ADMINISTRATION).

#### **Hepatic Impairment**

The pharmacokinetics of trametinib were characterized in 64 patients enrolled in clinical trials with trametinib who had mild hepatic impairment (defined by National Cancer Institute classification) using a population pharmacokinetic analysis. Trametinib oral clearance was not significantly different in these patients relative to patients with normal hepatic function. No data are available in patients with moderate or severe hepatic impairment (see DOSAGE REGIMEN AND ADMINISTRATION).

### **CLINICAL STUDIES**

#### **Unresectable or metastatic melanoma**

##### ***Meqsel monotherapy***

##### **Study MEK114267**

The efficacy and safety of Meqsel in patients with BRAF mutant unresectable or metastatic melanoma (V600E and V600K) were evaluated in a randomized open label study. Measurement of patients BRAF V600 mutation status was required. Screening included central testing of BRAF mutation (V600E and V600K) using a BRAF mutation assay conducted on the most recent tumur sample available.

Patients (N = 322) who were treatment naïve or may have received one prior chemotherapy treatment in the metastatic setting [Intent to Treat (ITT) population] were randomized 2:1 to receive trametinib 2 mg once daily or chemotherapy (dacarbazine 1000 mg/m<sup>2</sup> every 3 weeks or paclitaxel 175 mg/m<sup>2</sup> every 3 weeks). Treatment for all patients continued until disease progression, death or withdrawal.

The primary endpoint of the study was to evaluate the efficacy of trametinib compared to chemotherapy with respect to progression-free survival (PFS) in patients with advanced (unresectable or metastatic) BRAF V600E mutation-positive melanoma without a prior history of brain metastases (N = 273) which is considered the primary efficacy population. The secondary endpoints were progression-free survival in the ITT population and overall survival (OS), overall response rate (ORR), and duration of response (DoR) in the primary efficacy population and ITT population. Patients in the chemotherapy arm were allowed to cross-over to the trametinib arm after independent confirmation of progression. Fifty one (47 %) patients with confirmed disease progression in the chemotherapy arm crossed over to receive trametinib.

Baseline characteristics were balanced between treatment groups in the primary efficacy population and the ITT population. In the ITT population, the majority of patients were male (54 %) and all were Caucasian (100 %). The median age was 54 years (22 % were ≥ 65 years), most patients (64%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, and 11 patients (3 %) had a history of brain metastases. Most patients (87 %) in the ITT population had a BRAF V600E mutation and 12 % of patients had a BRAF V600K mutation. Most patients (66 %) had received no prior chemotherapy for advanced or metastatic disease.

The efficacy results in the primary efficacy population were consistent with those in the ITT population; therefore, only the efficacy data for the ITT population are presented in Table 6 and Figure 1.

**Table 6 MEK114267 - Investigator assessed efficacy results (ITT population).**

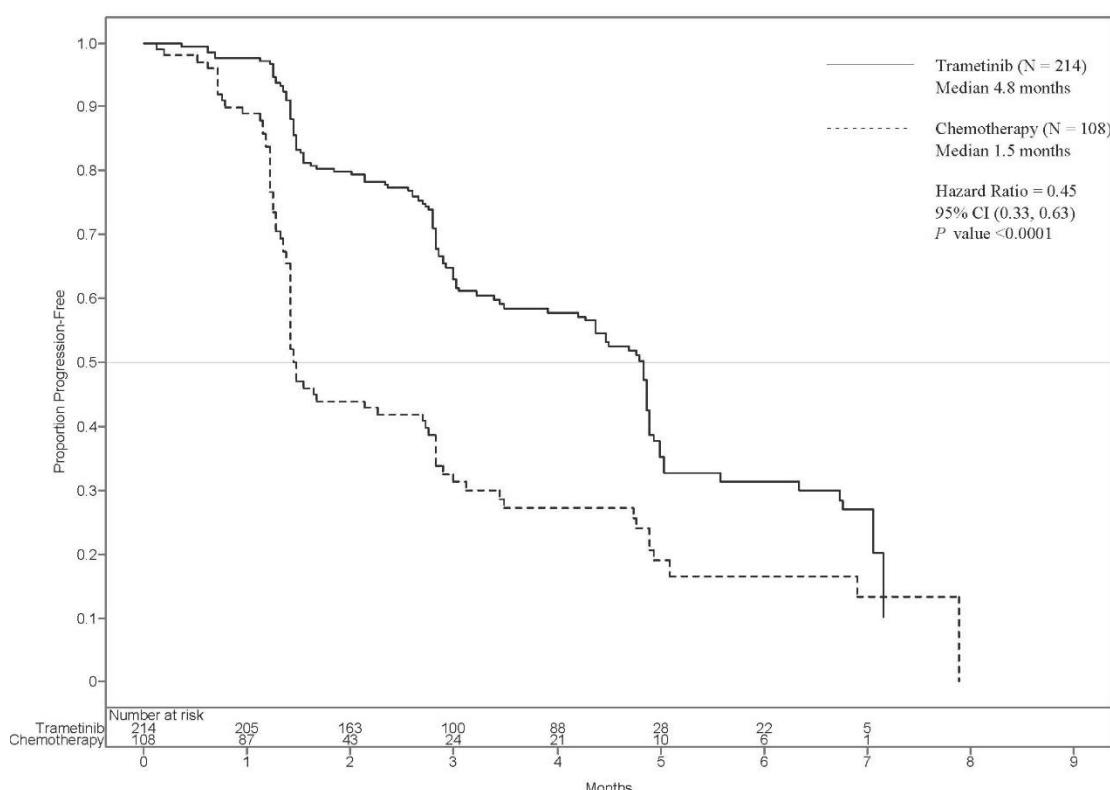
Endpoints/ Assessments	Intention-to-treat population	
	Trametinib (N=214)	Chemotherapy <sup>a</sup> (N=108)
<b>Progression-Free Survival</b>		
Median (months) (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
Hazard Ratio (95% CI)		0.45 (0.33, 0.63)
P value		<0.0001
<b>Overall Survival</b>		
Died, n (%)	35 (16)	29 (27)
Hazard Ratio (95% CI)		0.54 (0.32, 0.92)
P value		0.0136

Survival at 6 months (%) (95% CI)	81 (73, 86)	67 (55, 77)
Overall Response Rate (%)	22	8

ITT = Intent to Treat; PFS = Progression-free survival; CI = Confidence Interval.

<sup>a</sup>Chemotherapy included patients on dacarbazine (DTIC) 1000 mg/m<sup>2</sup> every 3 weeks or paclitaxel 175 mg/m<sup>2</sup> every 3 weeks.

**Figure 1 MEK114267 - Kaplan-Meier investigator-assessed progression-free survival curves (ITT population)**



The PFS result was consistent in the subgroup of patients with V600K mutation positive melanoma (HR = 0.50; [95 % CI: 0.18, 1.35], p=0.0788).

In a single arm Phase II study, Meqsel did not demonstrate clinical activity in patients who progressed on a prior BRAF inhibitor therapy in one of the cohorts (see INDICATIONS).

### **Meqsel in combination with Rafinlar**

The efficacy and safety of the recommended dose of Meqsel (2 mg once daily) in combination with Rafinlar (150mg twice daily) for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation were studied in two pivotal Phase III studies.

#### **MEK115306 (COMBI-d)**

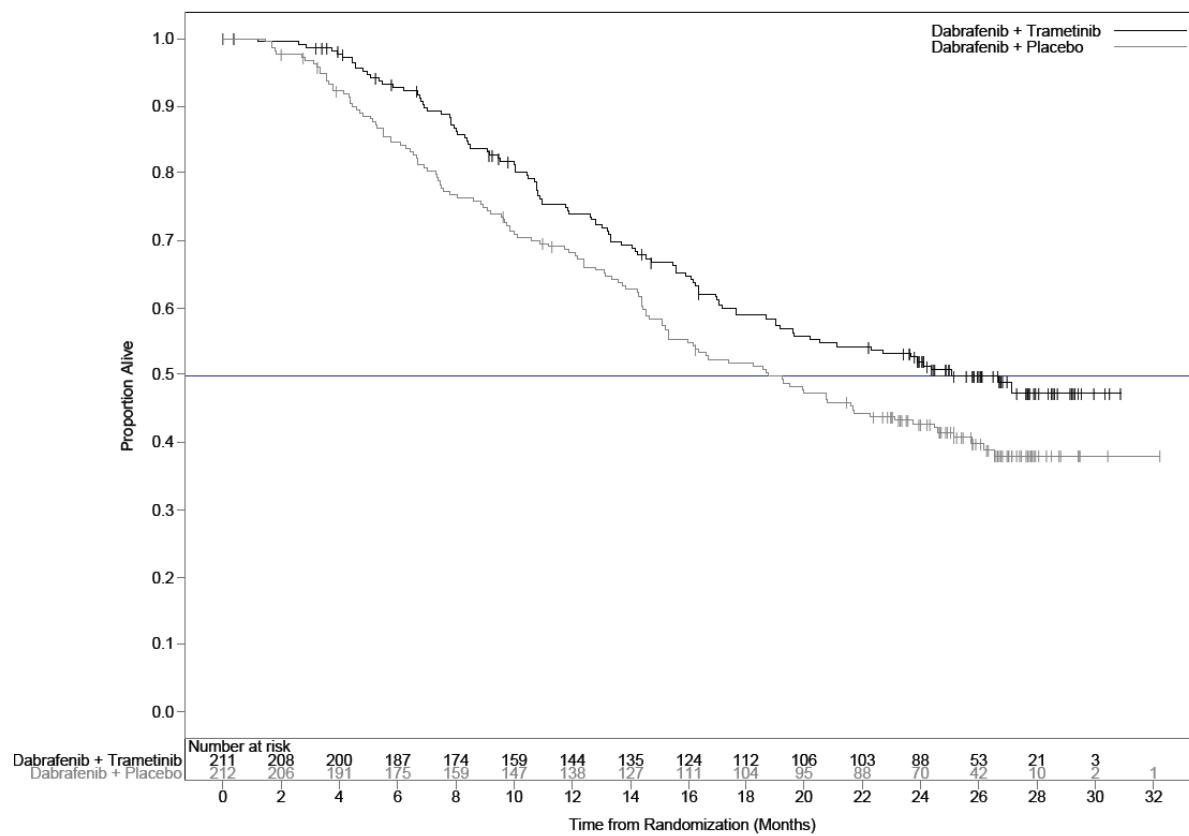
MEK115306 (COMBI-d) was a Phase III, randomized, double-blind study comparing the combination of Meqsel and dabrafenib to dabrafenib and placebo as first-line therapy for patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. The primary endpoint of the study was investigator assessed progression-free survival (PFS) with a key secondary endpoint of overall survival (OS). Patients were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ULN) and BRAF mutation (V600E versus V600K).

A total of 423 patients were randomized 1:1 to either the combination therapy arm (Meqsel 2 mg once daily and Rafinlar 150 mg twice daily) (N = 211) or dabrafenib monotherapy arm (150 mg twice daily) (N = 212). Baseline characteristics were balanced between treatment groups. Males constituted 53 % of patients and the median age was 56 years. The majority of patients had an ECOG performance score of 0 (72%) and had Stage IVM1c disease (66%). Most patients (85%) had the BRAF V600E mutation; the remaining 15% of patients had the BRAF V600K mutation.

At the time of final OS analysis, a total of 222 deaths (52.5%) [combination 99 deaths (47%) and dabrafenib 123 deaths (58%)] out of the randomized (or ITT) population were reported. The median follow up time on study treatment was 20 months in the combination therapy arm and 16 months in the dabrafenib monotherapy arm. Study MEK115306 showed a statistically significant 29% reduction in the risk of death for the combination therapy arm compared with the dabrafenib monotherapy arm (HR=0.71, 95% CI: 0.55, 0.92; p=0.011). The median OS was 25.1 months for the combination therapy arm and 18.7 months for the dabrafenib monotherapy arm. The 12-month (74%) and 24-month (51.4%) OS estimates for the combination were also greater than those for dabrafenib monotherapy (67.6 and 42.1%, respectively).

Extended follow-up found the 36-month OS estimate to be 44% for patients who received Meqsel in combination with Rafinlar and 32% for patients who received Rafinlar monotherapy.

**Figure 2: COMBI-d - Kaplan-Meier overall survival curves (ITT Population)**



Efficacy Results of PFS, ORR and Duration of Response are summarized in Table 7.

**Table 7 : Investigator-assessed efficacy results for MEK115306 (COMBI-d) study (primary data cut and final data cut):**

Endpoints	Primary Analysis*		Final Analysis*	
	Dabrafenib plus Trametinib N = 211	Dabrafenib N = 212	Dabrafenib plus Trametinib N = 211	Dabrafenib N = 212
Investigator Assessed PFS				
Progressive disease or death, n-(%)	102 (48)	109 ( 51)	139 (66)	162 (76)
Median, months (95% CI <sup>a</sup> )	9.3 (7.7, 11.1)	8.8 (5.9, 10.9)	11.0 (8.0, 13.9)	8.8 (5.9, 9.3)
Hazard Ratio (95% CI)	0.75 (0.57, 0.99)		0.67 ( 0.53, 0.84)	
P value (log-rank test)	0.035		<0.001	
Overall Response Rate <sup>b</sup> (%)	N=210 67 95% CI (59.9, 73.0)	N=210 51 (44.5,58.4)	N=210 69 (61.8, 74.8)	N=210 53 (46.3, 60.2)
Difference in response rate (CR <sup>c</sup> +PR <sup>c</sup> ), %	15 <sup>d</sup>		15 <sup>d</sup>	
95% CI for difference	5.9, 24.5		6.0, 24.5	
P value	0.0014		0.0014	
Duration of Response (months)				
Median (95% CI)	9.2 <sup>e</sup> (7.4, NR)	10.2 <sup>e</sup> (7.5, NR)	12.9 (9.4,19.5)	10.6 (9.1,13.8)

\*Primary data cut: 26 August 2013, Final data cut: 12 January 2015

a- Confidence interval

b- Overall Response Rate = Complete Response + Partial Response

c- CR: Complete Response, PR: Partial Response

d- ORR difference calculated based on the ORR result not rounded

e-At the time of the reporting the majority (≥59%) of investigator-assessed responses were still ongoing

NR = Not reached

### **MEK116513 (COMBI-v)**

Study MEK116513 was a two-arm, randomized, open-label, Phase III study comparing Meqsel and dabrafenib combination therapy with vemurafenib monotherapy in BRAF V600 mutation-positive unresectable or metastatic melanoma. The primary endpoint of the study was overall survival. patients were stratified by lactate dehydrogenase (LDH) level (> the upper limit of normal (ULN) versus ≤ ULN) and BRAF mutation (V600E versus V600K).

A total of 704 patients were randomized 1:1 to either the combination therapy arm (Meqsel 2 mg once daily and Rafinlar 150 mg twice daily) or the vemurafenib monotherapy arm (960 mg twice daily). Most patients were Caucasians (>96%) and male (55%), with a median age of 55 years (24% were ≥ 65 years). The majority of patients had Stage IV M1c disease (61%). Most patients had LDH ≤ULN (67%), ECOG performance status of 0 (70%), and visceral disease (78%) at baseline. Overall, 54%

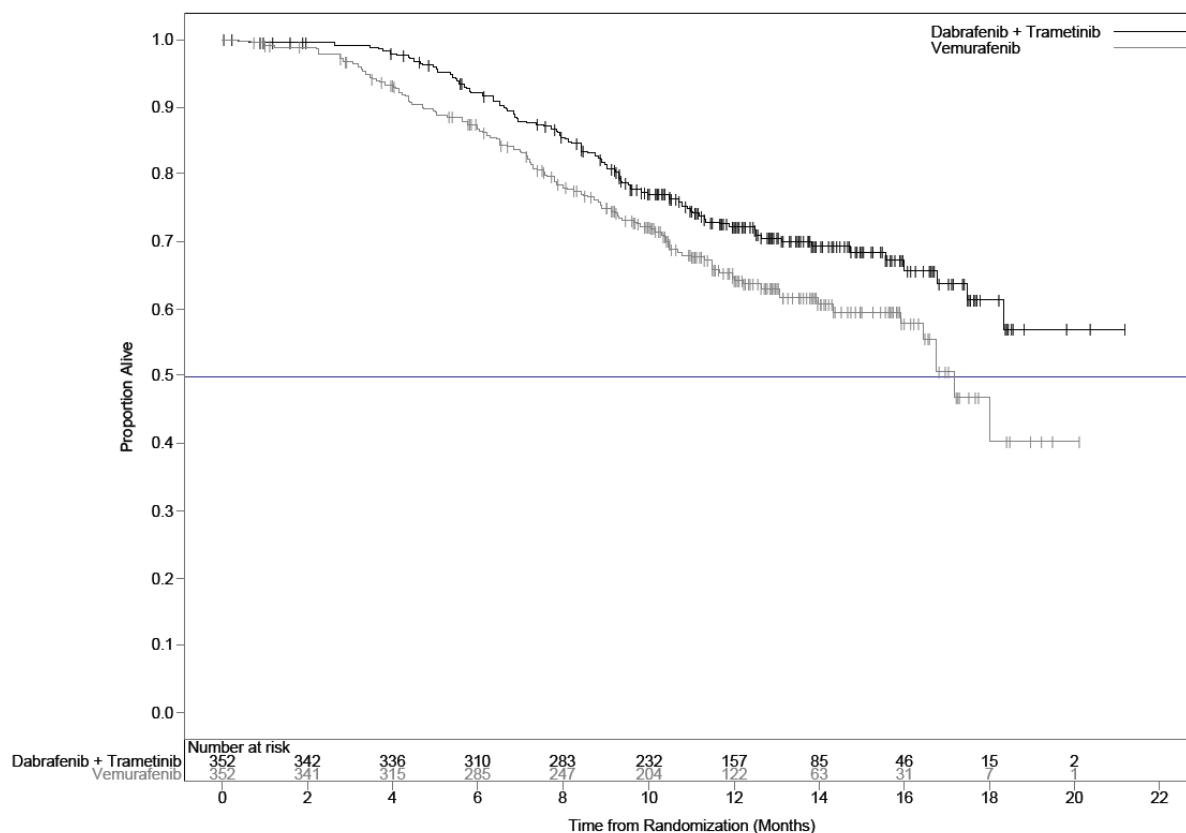
of patients had <3 disease sites at Baseline. The majority of patients had a BRAF V600E mutation (89%).

The OS analysis was conducted when 222 total deaths (77% of the required events for the final analysis) occurred. The Independent Data Monitoring Committee (IDMC) recommended stopping the study since the OS results crossed the pre-specified efficacy boundary. As a consequence the interim OS summary was considered the final comparative OS analysis.

The OS analysis for Study MEK116513 was based on 222 deaths (32%) [combination; 100 deaths (28%) and vemurafenib 122 deaths (35%)]. The median follow up time on study treatment was 11 months for the combination arm and 9 months in the vemurafenib arm. Study MEK116513 showed a statistically significant 31% reduction in the risk of death for the combination therapy compared with vemurafenib (HR=0.69, 95% CI: 0.53, 0.89; p=0.005). The median OS was not yet reached for the combination arm, and was 17.2 months for vemurafenib monotherapy.

Extended follow-up found the 36-month OS estimate to be 45% for patients who received Meqsel in combination with Rafinlar and 31% for patients who received vemurafenib monotherapy.

**Figure 3: COMBI-v - Kaplan-Meier overall survival curves (ITT Population)**



Results of the endpoints for PFS, ORR and Duration of response are summarized in Table 8.

**Table 8: Investigator- assessed efficacy results for MEK116513 (COMBI-v) study**

Endpoint	Dabrafenib + Trametinib (N=352)	Vemurafenib (N=352)
Investigator Assessed PFS		
Progressive disease or death, n- (%)	166 (47)	217 (62)
Median, months (95 % CI)	11.4 (9.9, 14.9)	7.3 (5.8, 7.8)
Hazard Ratio (95 % CI)		0.56 (0.46, 0.69)
P value		<0.001
Overall Response Rate, n (%) 95% CI	226 (64) (59.1, 69.4)	180 (51) (46.1, 56.8)
Difference in response rate (CR+PR), % (95% CI for difference)		13 (5.7, 20.2)
P value		0.0005
Duration of Response (months)		
Median (95% CI)	13.8 (11.0, NR)	7.5 (7.3, 9.3)

PFS= Progression Free Survival; NR= Not reached

### **BRF117277 / DRB436B2204 (COMBI-MB) – Metastatic melanoma patients with brain metastases**

The efficacy and safety of Meqsel in combination with Rafinlar in patients with BRAF mutant-positive melanoma that has metastasized to the brain was studied in a non-randomized open-label, multi-center Phase II study (COMBI-MB study).

A total of 125 patients were enrolled into four cohorts:

- Cohort A: patients with BRAFV600E mutant melanoma with asymptomatic brain metastases without prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort B: patients with BRAFV600E mutant melanoma with asymptomatic brain metastases with prior local brain-directed therapy and ECOG performance status of 0 or 1.
- Cohort C: patients with BRAFV600D/K/R mutant melanoma with asymptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1.

- Cohort D: patients with BRAFV600D/E/K/R mutant melanoma with symptomatic brain metastases, with or without prior local brain-directed therapy and ECOG performance status of 0 or 1 or 2.

The primary endpoint of the study was intracranial response in Cohort A, defined as the percentage of patients with a confirmed intracranial response assessed by the investigator using modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. Efficacy results are summarised in Table 10. Secondary endpoints were duration of intracranial response, ORR, PFS and OS. Efficacy results are summarized in Table 9.

**Table 9: COMBI-MB- Efficacy data by investigator assessment**

Endpoints/ assessment	All treated patients population			
	Cohort A N=76	Cohort B N=16	Cohort C N=16	Cohort D N=17
<b>Intracranial response rate, % (95 % CI)</b>				
	59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	59% (32.9, 81.6)
<b>Duration of intracranial response, median, months (95% CI)</b>				
	6.5 (4.9, 8.6)	7.3 (3.6, 12.6)	8.3 (1.3, 15.0)	4.5 (2.8, 5.9)
<b>ORR, % (95% CI)</b>				
	59% (47.3, 70.4)	56% (29.9, 80.2)	44% (19.8, 70.1)	65% (38.3, 85.8)
<b>PFS, median, months (95% CI)</b>				
	5.7 (5.3, 7.3)	7.2 (4.7, 14.6)	3.7 (1.7, 6.5)	5.5 (3.7, 11.6)
<b>OS, median, months (95% CI)</b>				
Median, months	10.8 (8.7, 17.9)	24.3 (7.9, NR)	10.1 (4.6, 17.6)	11.5 (6.8, 22.4)
CI = Confidence Interval NR = Not Reported				

## Advanced NSCLC

### Study E2201 BRF113928

The efficacy and safety of Meqsel in combination with dabrafenib was studied in a Phase II, three-cohort, multicenter, non-randomized, open-label study enrolling patients with stage IV BRAF V600E mutant NSCLC.

The primary endpoint was the investigator-assessed overall response rate ORR using the 'Response Evaluation Criteria In Solid Tumors' (RECIST 1.1 assessed by the investigator). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS), safety and population pharmacokinetics. ORR, DoR and PFS were also assessed by an Independent Review Committee (IRC) as a sensitivity analysis.

Cohorts were enrolled sequentially:

- Cohort A: Monotherapy (dabrafenib 150 mg twice daily): 84 patients enrolled. 78 patients had previous systemic treatment for their metastatic disease (see prescribing information for dabrafenib on results from Cohort A).
- Cohort B (n=57): Combination therapy (Meqsel 2 mg once daily and dabrafenib 150 mg twice daily): 59 patients enrolled. 57 patients had previously received one to three lines of systemic treatment for their metastatic disease. Two patients did not have any previous systemic treatment and were included in the analysis for patients enrolled in Cohort C.
- Cohort C (n=36): Combination therapy (Meqsel 2 mg once daily and dabrafenib 150 mg twice daily): 34 patients enrolled (note: the two patients from Cohort B that did not have any previous systemic treatment were included in the analysis for patients enrolled in Cohort C for a total of 36 patients.. All patients received study medication as first-line treatment for metastatic disease.

Among the total of 93 patients who were enrolled in the combination therapy in Cohorts B and C most patients were Caucasians (n=79, 85%). There was a similar female to male ratio (54% vs 46%). The median age was 64 years in patients who had at least one prior therapy and 68 years in patients who were treatment naïve for their advanced disease. Most patients (n=87, 94%) enrolled in the combination therapy treated Cohorts had an ECOG performance status of 0 or 1. Twenty-six (26) patients (28%) had never smoked. Ninety-one (91) patients (97.8%) had a non-squamous histology. In the pretreated population, 38patients (67%) had one line of systemic anti-cancer therapy for metastatic disease.

For the primary endpoint the investigator-assessed ORR, was 61.1% (95% CI, 43.5,76.9) in the first-line population and 66.7% (95% CI, 52.9%, 78.6%) in the previously treated population. These results met the statistical significance to reject the null hypothesis that the ORR of Meqsel in combination with Rafinlar for both NSCLC populations was less than or equal to 30%.

The ORR results assessed by IRC were consistent to the investigator assessment ([Table 10](#)).

The response was durable with median DoR in the previously treated population reaching 9.8 months (95% CI, 6.9, 16.0) by investigator assessment. For the first-line population, the median DoR and PFS could not yet be estimated (Table11), and 68% of patients with confirmed response were still ongoing in follow-up for duration of response.

**Table 10: Efficacy Results in Patients with BRAF V600E NSCLC**

Endpoint	Analysis	Combination First Line	Combination Second Line Plus
		N=36 <sup>1</sup>	N=57 <sup>1</sup>
Overall confirmed response n (%)	By Investigator	22 (61.1%)	38 (66.7%)

(95% CI)		(43.5, 76.9)	(52.9, 78.6)
	By IRC	22 (61.1%) (43.5, 76.9)	36 (63.2%) (49.3, 75.6)
Median DoR, months (95% CI)	By Investigator	NE <sup>2</sup> (8.3, NE)	9.8 (6.9, 16.0)
	By IRC	NE (6.9, NE)	12.6 (5.8, NE)
Median PFS, months (95% CI)	By Investigator	NE (7.0, NE)	10.2 (6.9, 16.7)
	By IRC	NE (7.0, NE)	8.6 (5.2, 16.8)
Median OS, months (95% CI)	-	24.6 (11.7, NE) <sup>3</sup>	18.2 (14.3, NE)

<sup>1</sup> Data cut-off: 8-Aug-2016  
<sup>2</sup> NE: Not Evaluable  
<sup>3</sup> Event rate for OS calculation was 28% and hence the defined median value still needs to mature

## NON-CLINICAL SAFETY DATA

### Safety pharmacology and repeat dose toxicity

In mice, lower heart rate, heart weight and left ventricular function were observed without cardiac histopathology after 3 weeks at  $\geq 0.25$  mg/kg/day trametinib (approximately three times human clinical exposure based on AUC) for up to three weeks. In adult rats, myocardial mineralization and necrosis associated with increased serum phosphorus were seen at doses  $\geq 1$  mg/kg/day (approximately 12 times human clinical exposure based on AUC). In juvenile rats, increased heart weight with no histopathology was observed at 0.35 mg/kg/day (approximately twice the adult human clinical exposure based on AUC).

Trametinib was phototoxic in an *in vitro* mouse fibroblast 3T3 Neutral Red Uptake (NRU) assay at significantly higher concentrations than clinical exposures (IC<sub>50</sub> at 2.92 microgram/mL,  $\geq 130$  times the clinical exposure based on C<sub>max</sub>), indicating that there is low risk for phototoxicity to patients taking trametinib.

In repeat-dose studies in rats, hepatocellular necrosis and transaminase elevations were seen after 8 weeks at  $\geq 0.062$  mg/kg/day (approximately 0.8 times human clinical exposure based on AUC).

### Carcinogenicity and mutagenicity

Carcinogenicity studies with trametinib have not been conducted. trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells and micronuclei in the bone marrow of rats.

## Reproductive Toxicity

### *Embryofetal development and fertility*

Trametinib may impair female fertility in humans. In adult and juvenile rat repeat dose studies with trametinib, alterations in follicular maturation, consisting of increases in cystic follicles and decreases in cystic corpora lutea, were observed at  $\geq 0.016$  mg/kg/day (approximately 0.3 times the human clinical exposure based on AUC).

Additionally, in juvenile rats given trametinib, decreased ovarian weights, slight delays in hallmarks of female sexual maturation (vaginal opening and increased incidence of prominent terminal end buds within the mammary gland) and slight hypertrophy of the surface epithelium of the uterus were observed. All of these effects were reversible following an off-treatment period and attributable to pharmacology. However, in rat and dog toxicity studies up to 13 weeks in duration, there were no treatment effects observed on male reproductive tissues.

## Juvenile animal studies

In a juvenile rat toxicity study, the principal toxicities in juvenile rats were on growth (bodyweight and long bone length), adverse microscopic findings included changes in the bone, mineralization and/or degeneration in various organs, primarily stomach at all doses. Adverse findings at the higher doses included in eye, kidney, aortic arch and/or nasal cavity/sinuses, heart, liver and in skin, and higher heart weights and the delay in a physical landmark of sexual maturity in females (vaginal opening).

The majority of findings are reversible with the exception of the bone, serum phosphorus and soft tissue mineralization which progressed/worsened during the off-drug period. Also, kidney tubular basophilia and higher heart weights were still present at end of recovery period.

With the exception of corneal mineralization/dystrophy and increased heart weight, similar effects have been observed in adult animals given trametinib. At the lowest combined dose level evaluated, the systemic exposure is approximately 0.3 times the human exposure at clinical dose of 2 mg/day based on AUC.

## Non-fixed dose combination therapy

### *Trametinib in combination with dabrafenib*

Dogs given trametinib and dabrafenib in combination for 4 weeks demonstrated similar toxicities to those observed in comparable monotherapy studies.

Refer to the full prescribing information for Rafinlar

## INCOMPATIBILITIES

Not applicable.

## STORAGE

See folding box.

Meqsel should not be used after the date marked "EXP" on the pack.



Meqsel must be kept out of the reach and sight of children.

#### **INSTRUCTIONS FOR USE AND HANDLING**

There are no special requirements for use or handling of this product.

#### **Manufacturer:**

See folding box.

#### **Further information is available from:**

Novartis Healthcare Private Limited

Inspire BKC, Part of 601 & 701,  
Bandra Kurla Complex, Bandra (East),  
Mumbai – 400 051, Maharashtra, India

Information issued: India pack insert dtd 5 Dec 2019 based on IPL dtd 12 Nov 18

**<sup>®</sup> = Registered Trademark of Novartis AG, Basel, Switzerland**

For the use of only Registered Medical Practitioners  
or a Hospital or a Laboratory.

## Ceritinib hard gelatin capsules 150 mg

### Spexib™

Protein kinase inhibitors

### DESCRIPTION AND COMPOSITION

#### Pharmaceutical form

#### Hard gelatin capsules

150 mg: Size #00 hard gelatin capsule with blue opaque cap with black imprint "LDK 150MG" and white opaque body with black imprint "NVR", containing white to almost white powder.

#### Active substance

Ceritinib

Each capsule contains 150 mg ceritinib.

#### Excipients

#### Hard gelatin capsule:

**Capsule content:** silica, colloidal anhydrous; low-substituted hydroxypropylcellulose; magnesium stearate; microcrystalline cellulose; sodium starch glycolate

**Capsule shell:** gelatin; indigotine (E132); titanium dioxide (E171)

**Printing ink:** ammonium hydroxide; iron oxide black (E172); propylene glycol; shellac glaze

### INDICATIONS

Spexib is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

Spexib as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).

### DOSAGE REGIMEN AND ADMINISTRATION

#### Dosage regimen

#### General target population

The recommended dose of Spexib is 450 mg taken orally once daily with food at the same time each day.

The maximum recommended dose is 450 mg taken orally once daily with food.

Continue treatment as long as the patient is deriving clinical benefit from therapy.

#### Dose adjustments

Temporary dose interruption and/or dose reduction of Spexib therapy may be required based on individual safety and tolerability. If dose reduction is required due to an adverse drug reaction not listed in Table 1, then the daily

dose of Spexib should be reduced by decrements of 150 mg. Early identification and management of adverse drug reactions with standard supportive care measures should be considered.

Spexib should be discontinued in patients unable to tolerate 150 mg taken once daily with food.

Table 1 summarizes recommendations for dose interruption, reduction, or discontinuation of Spexib in the management of selected adverse drug reactions (ADRs).

**Table 1 - Spexib dose adjustment and management recommendations for selected adverse drug reactions**

Criteria	Spexib Dosing
Severe or intolerable nausea, vomiting, or diarrhea despite optimal anti-emetic or anti-diarrheal therapy	Withhold Spexib until improved, then reinitiate Spexib by reducing dose by 150 mg
Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation greater than 5 times upper limit of normal (ULN) with concurrent total bilirubin less than or equal to 2times ULN	Withhold Spexib until recovery to baseline ALT/AST levels or to less than or equal to 3 times ULN, then reinitiate Spexib by reducing dose by 150 mg
ALT or AST elevation greater than 3 times ULN with concurrent total bilirubin elevation greater than 2 times ULN (in the absence of cholestasis or hemolysis)	Permanently discontinue Spexib
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue Spexib
QTc greater than 500 msec on at least 2 separate electrocardiograms (ECGs)	Withhold Spexib until recovery to baseline or to a QTc less than 481 msec, then reinitiate Spexib by reducing dose by 150 mg
QTc greater than 500 msec or greater than 60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	Permanently discontinue Spexib
Bradycardia <sup>a</sup> (symptomatic, may be severe and medically significant, medical intervention indicated)	<p>Withhold Spexib until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above</p> <p>Evaluate concomitant medications known to cause bradycardia, as well as anti-hypertensive medications</p> <p>If contributing concomitant medication is identified and discontinued, or its dose is adjusted, reinitiate Spexib at previous dose upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above</p> <p>If no contributing concomitant medication is identified, or if contributing concomitant medications are not discontinued or dose modified, reinitiate Spexib by reducing dose by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above</p>
Bradycardia <sup>a</sup> (life-threatening consequences, urgent intervention indicated)	<p>Permanently discontinue Spexib if no contributing concomitant medication is identified</p> <p>If contributing concomitant medication is identified and discontinued, or its dose is adjusted, reinitiate Spexib by reducing dose by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring<sup>b</sup></p>

Persistent hyperglycemia greater than 250 mg/dL despite optimal anti-hyperglycemic therapy	Withhold Spexib until hyperglycemia is adequately controlled, then reinstitute Spexib by reducing dose by 150 mg  If adequate glucose control cannot be achieved with optimal medical management, permanently discontinue Spexib
Elevated lipase or amylase greater than or equal to grade 3	Withhold Spexib until lipase or amylase returns to less than or equal to grade 1, then reinstitute by reducing dose by 150 mg
<sup>a</sup> Heart rate less than 60 beats per minute (bpm) <sup>b</sup> Permanently discontinue for recurrence	

### Strong CYP3A inhibitors

Avoid concurrent use of strong CYP3A inhibitors during treatment with Spexib (see section INTERACTIONS). If concomitant use of a strong CYP3A inhibitor is unavoidable, reduce the Spexib dose by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. After discontinuation of a strong CYP3A inhibitor, resume the Spexib dose that was taken prior to initiating the strong CYP3A inhibitor.

### Special populations

#### Renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Caution should be used in patients with severe renal impairment as there is no experience with Spexib in this population (see section CLINICAL PHARMACOLOGY).

#### Hepatic impairment

For patients with severe hepatic impairment (Child-Pugh C), reduce the dose of Zykadia by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. No dose adjustment is necessary in patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. (see section CLINICAL PHARMACOLOGY).

#### Pediatric patients (below 18 years)

The safety and efficacy of Spexib have not been established in pediatric patients.

#### Geriatric patients (65 years or above)

The limited data on the safety and efficacy of Spexib in patients aged 65 years and older do not suggest that a dose adjustment is required in elderly patients (see section CLINICAL PHARMACOLOGY).

#### Method of administration

Spexib should be administered orally once daily with food at the same time every day. Food can range from a snack to a full meal (see section INTERACTIONS and section CLINICAL PHARMACOLOGY). Spexib capsules should be swallowed whole with water. The capsules should not be chewed or crushed.

If a dose is missed, the patient should make up that dose, unless the next dose is due within 12 hours. If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose.

### CONTRAINDICATIONS

None.

## **WARNINGS AND PRECAUTIONS**

### **Hepatotoxicity**

Cases of hepatotoxicity occurred in 1.1 % of patients treated with Spexib in clinical studies (see section ADVERSE DRUG REACTIONS). Increases to grade 3 or 4 ALT elevations were observed in 25% of patients receiving Spexib. Concurrent elevations in ALT/AST greater than three times the upper limit of normal and total bilirubin greater than two times the upper limit of normal, with normal alkaline phosphatase, occurred in less than 1% of patients in clinical studies. The majority of cases were manageable with dose interruption and/or dose reduction. Few events required discontinuation of Spexib.

Monitor with liver laboratory tests (including ALT, AST, and total bilirubin) prior to the start of treatment and monthly thereafter. In patients who develop transaminase elevations, more frequent monitoring of liver transaminases and total bilirubin should be done as clinically indicated (see section DOSAGE REGIMEN AND ADMINISTRATION).

### **Interstitial lung disease (ILD)/Pneumonitis**

Severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been observed in patients treated with Spexib in clinical studies (see section ADVERSE DRUG REACTIONS). Most of these severe/life-threatening cases improved or resolved with interruption of Spexib.

Monitor patients for pulmonary symptoms indicative of pneumonitis. Exclude other potential causes of ILD/pneumonitis, and permanently discontinue Spexib in patients diagnosed with any grade treatment-related ILD/pneumonitis (see section DOSAGE REGIMEN AND ADMINISTRATION).

### **QT interval prolongation**

QTc prolongation has been observed in clinical studies in patients treated with Spexib, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de pointes) or sudden death (see section ADVERSE DRUG REACTIONS). A categorical outlier analysis of ECG data demonstrated new QTc >500 msec in 12 patients (1.3%), among which six had elevated QTc>450 msec at baseline. There were 58 patients (4.46.3%) with a QTc increase from baseline >60 msec. A pharmacokinetic/pharmacodynamic analysis suggested that ceritinib causes concentration-dependent increases in QTc.

Avoid use of Spexib in patients with congenital long QT syndrome. Periodic monitoring with ECGs and periodic monitoring of electrolytes (e.g., potassium) is recommended in patients with congestive heart failure, bradyarrhythmias, or electrolyte abnormalities and in patients who are taking medications that are known to prolong the QT interval. In case of vomiting, diarrhea, dehydration, or impaired renal function, correct electrolytes as clinically indicated. Permanently discontinue Spexib in patients who develop QTc greater than 500 msec or greater than 60 msec change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia. Withhold Spexib in patients who develop QTc greater than 500 msec on at least 2 separate ECGs until recovery to baseline or a QTc less than 481 msec, then reinitiate Spexib by reducing dose by 150 mg (see section DOSAGE REGIMEN AND ADMINISTRATION and section CLINICAL PHARMACOLOGY).

### **Bradycardia**

Asymptomatic cases of bradycardia have been observed in patients treated with Spexib in clinical studies (see section ADVERSE DRUG REACTIONS).

Avoid use of Spexib in combination with other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Monitor heart rate and blood pressure regularly. In cases of symptomatic bradycardia that is not life-threatening, withhold Spexib until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, evaluate the use of concomitant medications, and adjust the dose of Spexib if necessary. Permanently discontinue Spexib for life-threatening bradycardia if no contributing concomitant medication is identified; however, if associated with concomitant medication known to cause bradycardia or hypotension, withhold Spexib until recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, and if concomitant medication can be adjusted or discontinued, reinitiate Spexib by reducing dose by 150 mg upon recovery to asymptomatic bradycardia or to a heart rate of 60 bpm or above, with frequent monitoring (see section DOSAGE REGIMEN AND ADMINISTRATION).

### **Gastrointestinal adverse reactions**

Diarrhea, nausea, or vomiting occurred in 74.2% of 89 patients treated with Spexib at the recommended dose of 450 mg taken with food in a dose optimization study A2112 (ASCEND-8) and were mainly grade 1 events (49.4%). One patient (1.1%) experienced grade 3 diarrhea. Seven patients (7.9%) required study drug interruption due to diarrhea or nausea. No patients required dose reduction or discontinuation of Spexib due to diarrhea, nausea, or vomiting (see section ADVERSE DRUG REACTIONS).

Monitor and manage patients using standards of care, including anti-diarrheals, anti-emetics, or fluid replacement, as indicated. Dose interruption and dose reduction may be employed as necessary. If vomiting occurs during the course of treatment, the patient should not take an additional dose, but should continue with the next scheduled dose (see section DOSAGE REGIMEN AND ADMINISTRATION).

### **Hyperglycemia**

Events of hyperglycemia (all grades) have been reported in less than 10% of patients treated with Spexib in clinical studies; 5% of patients reported a grade 3/4 event (see section ADVERSE DRUG REACTIONS). The risk of hyperglycemia was higher in patients with diabetes mellitus and/or concurrent steroid use.

Monitor fasting serum glucose prior to the start of Spexib treatment and periodically thereafter as clinically indicated. Initiate or optimize anti-hyperglycemic medications as indicated (see section DOSAGE REGIMEN AND ADMINISTRATION).

### **Lipase and/or amylase elevations**

Elevations of lipase and/or amylase have occurred in patients receiving Spexib in clinical studies (see section ADVERSE DRUG REACTIONS).

Monitor lipase and amylase prior to the start of Spexib treatment and periodically thereafter as clinically indicated (see section DOSAGE REGIMEN AND ADMINISTRATION).

## **ADVERSE DRUG REACTIONS**

### **Summary of the safety profile**

Adverse drug reactions described below reflect exposure to Spexib 750 mg once daily fasted in 925 patients with ALK-positive advanced NSCLC across a pool of seven clinical studies, including two randomized, active-controlled, Phase 3 studies (Studies A2301 and A2303).

The median duration of exposure to Spexib 750 mg fasted was 44.9 weeks (range 0.1 to 200.1 weeks). Dose reductions occurred in 62.2% of patients and dose interruptions in 74.8% of patients. The rate of adverse events (AEs) resulting in permanent discontinuation of Spexib was 12.1%. The most frequent AEs (>0.5%) leading to discontinuation of Spexib were pneumonia (0.6%) and respiratory failure (0.6%).

Adverse drug reactions (ADRs) with an incidence of  $\geq 10\%$  in patients treated with Spexib 750 mg fasted were diarrhoea, nausea, vomiting, liver laboratory test abnormalities, fatigue, abdominal pain, decreased appetite, weight decreased, constipation, blood creatinine increased, rash, anaemia and esophageal disorder.

Grade 3/4 ADRs with an incidence of  $\geq 5\%$  in patients treated with Spexib 750 mg fasted were liver laboratory test abnormalities, fatigue, vomiting, hyperglycaemia, nausea and diarrhoea.

In the dose optimization study A2112 (ASCEND-8) in both previously treated and untreated patients with ALK-positive advanced NSCLC, the overall safety profile of Spexib at the recommended dose of 450 mg with food (N=89) was consistent with Spexib 750 mg fasted (N=90), except for a reduction in gastrointestinal adverse drug reactions, while achieving comparable steady-state exposure (see section CLINICAL PHARMACOLOGY). The incidence and severity of gastrointestinal adverse drug reactions (diarrhoea 56%, nausea 45%, vomiting 35%; 1.1% reported a grade 3/4 event) were reduced for patients treated with Spexib 450 mg with food compared to 750 mg fasted (diarrhoea 76%, nausea 50%, vomiting 56%; 12% reported a grade 3/4 event). In patients treated with Spexib 450 mg with food, 10% of patients had at least one adverse event that required dose reduction and 42% of patients had at least one adverse event that required study drug interruption.

## Tabulated summary of adverse drug reactions from clinical trials

Table 2 presents the frequency category of ADRs reported for Spebib in patients treated at a dose of 750 mg fasted (N=925) in 7 clinical studies. The frequency of selected gastrointestinal ADRs (diarrhoea, nausea and vomiting) are based on patients treated with a dose of 450 mg once daily with food (N=89).

ADRs are listed according to MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); and not known (cannot be estimated from the available data).

**Table 2 Adverse drug reactions in patients (N=925) treated with Spebib**

Primary System Organ Class Preferred Term	All grades n (%)	Frequency category	Grades 3/4 n (%)	Frequency category
<b>Blood and lymphatic system disorders</b>				
Anaemia	141 (15.2)	Very Common	28 (3.0)	Common
<b>Metabolism and nutrition disorders</b>				
Decreased appetite	365 (39.5)	Very common	20 (2.2)	Common
Hyperglycaemia	87 (9.4)	Common	50 (5.4)	Common
Hypophosphataemia	49 (5.3)	Common	21 (2.3)	Common
<b>Eye disorders</b>				
Vision disorder <sup>m</sup>	65 (7.0)	Common	0	
<b>Cardiac disorders</b>				
Pericarditis <sup>h</sup>	54 (5.8)	Common	24 (2.6)	Common
Bradycardia <sup>e</sup>	21 (2.3)	Common	0	
<b>Respiratory, thoracic and mediastinal disorders</b>				
Pneumonitis <sup>i</sup>	19 (2.1)	Common	11 (1.2)	Common
<b>Gastrointestinal disorders</b>				
Diarrhoea <sup>n</sup>	50 (56.2)	Very common	1 (1.1)	Common
Nausea <sup>n</sup>	40 (44.9)	Very common	0	
Vomiting <sup>n</sup>	31 (34.8)	Very common	0	
Abdominal pain <sup>a</sup>	426 (46.1)	Very common	23 (2.5)	Common
Constipation	222 (24.0)	Very common	3 (0.3)	Uncommon
Oesophageal disorder <sup>f</sup>	130 (14.1)	Very common	4 (0.4)	Uncommon
Pancreatitis	5 (0.5)	Uncommon	5 (0.5)	Uncommon
<b>Hepatobiliary disorders</b>				
Abnormal liver function tests <sup>c</sup>	20 (2.2)	Common	9 (1.0)	Common
Hepatotoxicity <sup>d</sup>	10 (1.1)	Common	4 (0.4)	Uncommon
<b>Skin and subcutaneous tissue disorders</b>				
Rash <sup>j</sup>	181 (19.6)	Very common	4 (0.4)	Uncommon
<b>Renal and urinary disorders</b>				
Renal failure <sup>k</sup>	17 (1.8)	Common	2 (0.2)	Uncommon
Renal impairment <sup>l</sup>	9 (1.0)	Common	1 (0.1)	Uncommon
<b>General disorders and administration site conditions</b>				
Fatigue <sup>g</sup>	448 (48.4)	Very common	71 (7.7)	Common
<b>Investigations</b>				
Liver laboratory test	560 (60.5)	Very common	347 (37.5)	Very common

Primary System Organ Class Preferred Term	All grades n (%)	Frequency category	Grades 3/4 n (%)	Frequency category
abnormalities <sup>b</sup>				
Weight decreased	255 (27.6)	Very common	26 (2.8)	Common
Blood creatinine increased	204 (22.1)	Very common	5 (0.5)	Uncommon
Electrocardiogram QT prolonged	90 (9.7)	Common	19 (2.1)	Common
Lipase increased	44 (4.8)	Common	32 (3.5)	Common
Amylase increased	65 (7.0)	Common	29 (3.1)	Common

<sup>a</sup> Abdominal pain includes PTs of Abdominal Pain, Abdominal Pain Upper, Abdominal Discomfort, Epigastric Discomfort

<sup>b</sup> Liver laboratory test abnormalities includes PTs of Alanine Aminotransferase Increased, Aspartate Aminotransferase Increased, Gamma-Glutamyltransferase Increased, Blood Bilirubin Increased, Transaminases Increased, Hepatic Enzyme Increased, Liver Function Test Abnormal, Liver Function Test Increased, Blood Alkaline Phosphatase Increased

<sup>c</sup> Abnormal liver function tests includes PTs of Hepatic Function Abnormal, Hyperbilirubinaemia

<sup>d</sup> Hepatotoxicity includes PTs of Drug-Induced Liver Injury, Hepatitis Cholestatic, Hepatocellular Injury, Hepatotoxicity

<sup>e</sup> Bradycardia includes PTs of Bradycardia and Sinus Bradycardia

<sup>f</sup> Esophageal Disorder includes PTs of Dyspepsia, Gastroesophageal Reflux Disease, Dysphagia

<sup>g</sup> Fatigue includes PTs of Fatigue and Asthenia

<sup>h</sup> Pericarditis includes PTs of Pericardial Effusion and Pericarditis

<sup>i</sup> Pneumonitis includes PTs of Interstitial Lung Disease (ILD) and Pneumonitis

<sup>j</sup> Rash includes PTs of Rash, Dermatitis Acneiform, Rash Maculo-Papular

<sup>k</sup> Renal Failure includes PTs of Acute Renal Injury and Renal Failure

<sup>l</sup> Renal Impairment includes PTs of Azotaemia and Renal Impairment

<sup>m</sup> Vision disorder includes PTs of Visual Impairment, Vision Blurred, Photopsia, Vitreous Floaters, Visual Acuity Reduced, Accommodation Disorder, Presbyopia

<sup>n</sup> The frequency of these selected gastrointestinal ADRs (diarrhoea, nausea and vomiting) is based on patients treated with the recommended dose of 450 mg with food (N=89) in Study A2112 (ASCEND-8)

## Special populations

### Geriatric population

Across seven clinical studies, 168 of 925 patients (18.2%) treated with Spebib were aged 65 years and older. The safety profile in patients aged 65 years and older was similar to that in patients less than 65 years of age (see section DOSAGE REGIMEN AND ADMINISTRATION).

## INTERACTIONS

### Agents that may increase ceritinib plasma concentrations

#### Strong CYP3A inhibitors

In healthy subjects, co-administration of a single 450 mg fasted ceritinib dose with ketoconazole (200 mg twice daily for 14 days), a strong CYP3A/P-gp inhibitor, resulted in 2.9-fold and 1.2-fold increase in ceritinib AUCinf and C<sub>max</sub>, respectively, compared to when ceritinib was given alone. The steady-state AUC of ceritinib at reduced doses after co-administration with ketoconazole 200 mg twice daily for 14 days was predicted by simulations to be similar to the steady-state AUC of ceritinib alone.

Avoid concurrent use of strong CYP3A inhibitors during treatment with Spebib. If concomitant use of strong CYP3A inhibitors is unavoidable, including but not limited to, ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, and nefazodone, reduce the Spebib dose by approximately one-third, rounded to the nearest multiple of the 150 mg dosage strength. After discontinuation of a strong CYP3A

inhibitor, resume the Spebib dose that was taken prior to initiating the strong CYP3A inhibitor (see section DOSAGE REGIMEN AND ADMINISTRATION).

#### **P-gp inhibitors**

Based on *in vitro* data, ceritinib is a substrate of the efflux transporter P-glycoprotein (P-gp). If Spebib is administered with drugs that inhibit P-gp, an increase in ceritinib concentration is likely. Exercise caution with concomitant use of P-gp inhibitors and carefully monitor adverse drug reactions.

#### **Agents that may decrease ceritinib plasma concentrations**

##### **Strong CYP3A and P-gp inducers**

In healthy subjects, co-administration of a single 750 mg fasted ceritinib dose with rifampin (600 mg daily for 14 days), a strong CYP3A/P-gp inducer, resulted in 70% and 44% decreases in ceritinib AUC<sub>inf</sub> and C<sub>max</sub>, respectively, compared to when ceritinib was given alone. Co-administration of Spebib with strong CYP3A/P-gp inducers decreases ceritinib plasma concentrations. Avoid concomitant use of strong CYP3A inducers, including but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, and St. John's Wort (*Hypericum perforatum*). Exercise caution with concomitant use of P-gp inducers.

#### **Agents whose plasma concentration may be altered by ceritinib**

##### **CYP3A and CYP2C9 substrates**

Based on *in vitro* data, ceritinib competitively inhibits the metabolism of a CYP3A substrate, midazolam, and a CYP2C9 substrate, diclofenac. Time-dependent inhibition of CYP3A was also observed.

Co-administration of a single dose of midazolam (a sensitive CYP3A substrate) following 3 weeks of Spebib dosing in patients (750 mg daily fasted) increased the midazolam AUC<sub>inf</sub> (90% CI) by 5.4-fold (4.6, 6.3) compared to midazolam alone. Avoid co-administration of Spebib with substrates primarily metabolized by CYP3A or CYP3A substrates known to have narrow therapeutic indices (e.g., cyclosporin, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, tacrolimus, alfentanil and sirolimus). If unavoidable, consider dose reduction for co-administered medicines that are CYP3A substrates with narrow therapeutic indices.

Co-administration of a single dose of warfarin (a CYP2C9 substrate) following 3 weeks of Spebib dosing in patients (750 mg daily fasted) increased the S-warfarin AUC<sub>inf</sub> (90% CI) by 54% (36%, 75%) compared to warfarin alone. Avoid co-administration of Spebib with substrates primarily metabolized by CYP2C9 or CYP2C9 substrates known to have narrow therapeutic indices (e.g., phenytoin and warfarin). If unavoidable, consider dose reduction for co-administered medicines that are CYP2C9 substrates with narrow therapeutic indices. Increase the frequency of international normalized ratio (INR) monitoring if co-administration with warfarin is unavoidable as the anti-coagulant effect of warfarin may be enhanced.

##### **CYP2A6 and CYP2E1 substrates**

Based on *in vitro* data, ceritinib also inhibits CYP2A6 and CYP2E1 at clinically relevant concentrations. Therefore, ceritinib may have the potential to increase plasma concentrations of co-administered drugs that are predominantly metabolized by these enzymes. Exercise caution with concomitant use of CYP2A6 and CYP2E1 substrates and carefully monitor adverse drug reactions.

#### **Agents that are substrates of transporters**

Based on *in vitro* data, ceritinib does not inhibit apical efflux transporters, BCRP, P-gp or MRP2, hepatic uptake transporters OATP1B1 or OATP1B3, renal organic anion uptake transporters OAT1 and OAT3, or the organic cation uptake transporters OCT1 or OCT2 at clinically relevant concentrations. Therefore, clinical drug-drug interactions as a result of ceritinib-mediated inhibition of substrates for these transporters are unlikely to occur.

#### **Agents that affect gastric pH**

Gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids) may alter the solubility of ceritinib and reduce its bioavailability as ceritinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro*. In a drug interaction study in healthy subjects (N=22), co-administration of a single dose of 750 mg of ceritinib fasted and esomeprazole (a proton pump inhibitor) at 40 mg daily for 6 days decreased the ceritinib exposure (AUC<sub>inf</sub> and C<sub>max</sub> decreased by 76% and 79%, respectively). However, coadministration of a single 750 mg ceritinib dose fasted with proton pump inhibitors for 6 days in a subgroup of patients from Study X2101 suggested less effect on ceritinib exposure than that observed in healthy subjects as AUC (90% CI) decreased by 30% (0%, 52%) and C<sub>max</sub> (90% CI) decreased by

25% (5%, 41%) and no clinically meaningful effect on ceritinib exposure was observed at steady-state after ceritinib once daily dosing.

This is further confirmed by a subgroup analysis based on three clinical studies (N >400) in which patients with and without proton pump inhibitors showed similar steady-state exposure and clinical efficacy and safety.

#### **Drug-food/drink interactions**

Spebib should be taken with food. The bioavailability of ceritinib is increased in the presence of food (see section CLINICAL PHARMACOLOGY).

Patients should be instructed to avoid grapefruit or grapefruit juice as they may inhibit CYP3A in the gut wall and may increase the bioavailability of ceritinib.

### **PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL**

#### **Pregnancy**

##### **Risk summary**

There are insufficient data regarding the use of Spebib in pregnant women. Reproductive toxicology studies (i.e., embryo-fetal development studies) in pregnant rats and rabbits indicated no fetotoxicity or teratogenicity after dosing with ceritinib during organogenesis; however, maternal plasma exposure was less than that observed at the recommended human dose. The potential risk in humans is unknown. Spebib should not be given to pregnant women unless the potential benefit outweighs the potential risk to the fetus.

#### **Lactation**

##### **Risk Summary**

It is unknown whether ceritinib is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse drug reactions in breastfed newborns/infants, a decision should be made whether to discontinue breast-feeding or discontinue using Spebib taking into account the importance of Spebib to the mother.

#### **Females and males of reproductive potential**

##### **Contraception**

##### **Females**

Females of reproductive potential should be advised to use an effective method of contraception (methods that result in less than 1% pregnancy rates) while receiving Spebib and for up to 3 months after discontinuing treatment.

##### **Infertility**

Formal non-clinical studies on the potential effects of ceritinib on fertility have not been conducted. The potential for Spebib to cause infertility in male and female patients is unknown.

### **OVERDOSAGE**

There is limited reported experience with overdose in humans. General supportive measures should be initiated in all cases of overdose.

### **CLINICAL PHARMACOLOGY**

#### **Mechanism of action (MOA)**

Ceritinib is an orally highly selective and potent ALK kinase inhibitor. Ceritinib inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells both *in vitro* and *in vivo*.

ALK translocation determines expression of the resulting fusion protein and consequent aberrant ALK signaling in NSCLC. In the majority of NSCLC cases, EML4 is the translocation partner for ALK; this generates an EML4-ALK fusion protein containing the protein kinase domain of ALK fused to the N-terminal part of EML4. Ceritinib was demonstrated effective against EML4-ALK kinase activity in a NSCLC cell line (H2228), resulting in inhibition of cell proliferation *in vitro* and regression of tumors in H2228 derived xenografts in mouse and rat.

### **Pharmacodynamics (PD)**

Ceritinib inhibition of ALK kinase activity and ALK-mediated signaling pathways in Karpas 299 (lymphoma cell line) and in H2228 (lung cancer cell line) was demonstrated to be dose-dependent. The inhibitory effect of ceritinib led to inhibition of cancer cell proliferation *in vitro* and tumor regression *in vivo* in mouse and rat xenograft models. Ceritinib is approximately 20-fold more potent than crizotinib in enzymatic inhibition assays of the ALK kinase activity (IC<sub>50</sub> for inhibition of ALK of 0.15 nanomolar for ceritinib and 3 nanomolar for crizotinib). In a kinase panel of 36 enzymes, ceritinib inhibited only 2 other kinases with approximately 50-fold less potency for ALK inhibition. All other kinases in the panel had greater than 500-fold less potency when compared with ALK, demonstrating a high degree of selectivity. A single-dose pharmacodynamic study and multiple-daily dose efficacy study performed in Karpas 299 lymphoma and H2228 lung cancer tumor models indicated that a 60% to 80% reduction in the ALK signaling pathway may be required to achieve tumor regression.

### **Pharmacokinetics (PK)**

#### **Absorption**

Peak plasma levels ( $C_{\max}$ ) of ceritinib are achieved approximately 4 to 6 hours after a single oral administration in patients. Oral absorption was estimated to be  $\geq 25\%$  based on metabolite percentages in the feces. The absolute bioavailability of ceritinib has not been determined.

Daily oral dosing of ceritinib results in achievement of steady-state by approximately 15 days and remains stable afterwards, with a geometric mean accumulation ratio of 6.2 after 3 weeks of daily dosing.

After a single oral administration of ceritinib in patients, plasma exposure to ceritinib, as represented by  $C_{\max}$  and  $AUC_{\text{last}}$ , increased dose-proportionally over the 50 to 750 mg dose range under fasted conditions. In contrast with single-dose data, pre-dose concentration ( $C_{\min}$ ) after repeated daily dosing appeared to increase in a greater than dose-proportional manner.

#### **Food effect:**

Systemic exposure of ceritinib was increased when administered with food. Ceritinib  $AUC_{\text{inf}}$  values were approximately 58% and 73% higher ( $C_{\max}$  approximately 43% and 41% higher) in healthy subjects when a single 500 mg ceritinib dose (capsule) was administered with a low fat meal (containing approximately 330 calories and 9 grams of fat) and a high fat meal (containing approximately 1000 calories and 58 grams of fat), respectively, as compared with the fasted state.

Systemic exposure of ceritinib was increased when administered with food. Ceritinib  $AUC_{\text{inf}}$  values were approximately 39% and 64% higher ( $C_{\max}$  approximately 42% and 58% higher) in healthy subjects when a single 750 mg ceritinib dose (tablet) was administered with a low fat meal (containing approximately 330 calories and 9 grams of fat) and a high fat meal (containing approximately 1000 calories and 58 grams of fat), respectively, as compared with the fasted state.

In a dose optimization study A2112 (ASCEND-8) in patients comparing Spexib 450 mg or 600 mg daily with food (approximately 100 to 500 calories and 1.5 to 15 grams of fat) to 750 mg daily under fasted conditions, there was no clinically meaningful difference in the systemic steady-state exposure of ceritinib for the 450 mg with food arm (N=36) compared to the 750 mg fasted arm (N=31), with only small increases in steady-state  $AUC$  (90% CI) by 4% (-13%, 24%) and  $C_{\max}$  (90% CI) by 3% (-14%, 22%). In contrast, the steady-state  $AUC$  (90% CI) and  $C_{\max}$  (90% CI) for the 600 mg with food arm (N=30) increased by 24% (3%, 49%) and 25% (4%, 49%), respectively, compared to the 750 mg fasted arm. The maximum recommended dose of Spexib is 450 mg taken orally once daily with food (see section DOSAGE REGIMEN AND ADMINISTRATION).

## **Distribution**

Binding of ceritinib to human plasma proteins *in vitro* is approximately 97% in a concentration independent manner, from 50 ng/mL to 10,000 ng/mL. The apparent volume of distribution (Vd/F) is 4230 L in patients after a single 750 mg fasted dose of Spebib. Ceritinib also has a slight preferential distribution to red blood cells, relative to plasma, with a mean *in vitro* blood-to-plasma ratio of 1.35. *In vitro* studies suggest that ceritinib is a substrate for P-glycoprotein (P-gp), but not of breast cancer resistance protein (BCRP) or multi-resistance protein 2 (MRP2). The *in vitro* apparent passive permeability of ceritinib was determined to be low.

In rats, ceritinib crosses the intact blood brain barrier with a brain-to-blood exposure (AUC<sub>inf</sub>) ratio of about 15%. There are no data related to brain-to-blood exposure ratio in humans.

## **Biotransformation/metabolism**

*In vitro* studies demonstrated that CYP3A was the major enzyme involved in the metabolic clearance of ceritinib.

Following a single oral administration of radioactive ceritinib dose at 750 mg fasted, ceritinib was the main circulating component (82%) in human plasma. A total of 11 metabolites were found circulating in plasma at low levels with mean contribution to the radioactivity AUC of ≤2.3% for each metabolite. Main biotransformation pathways identified in healthy subjects included mono-oxygenation, O-dealkylation, and N-formylation. Secondary biotransformation pathways involving the primary biotransformation products included glucuronidation and dehydrogenation. Addition of a thiol group to O-dealkylated ceritinib was also observed.

## **Elimination**

Following single oral doses of ceritinib under fasted conditions, the geometric mean apparent plasma terminal half-life (T<sub>1/2</sub>) of ceritinib ranged from 31 to 41 hours in patients over the 400 to 750 mg dose range. The geometric mean apparent clearance (CL/F) of ceritinib was lower at steady-state (33.2 L/hr) after 750 mg daily oral dosing than after a single 750 mg oral dose (88.5 L/hr) suggesting that ceritinib demonstrates non-linear PK over time.

The primary route of excretion of ceritinib and its metabolites is in the feces. Recovery in the feces accounts for 91% of the administered oral dose (with a mean 68% of an oral dose as unchanged parent compound). Only 1.3% of the administered oral dose is recovered in the urine.

## **Special populations**

### **Effects of age, gender, and race**

Population pharmacokinetic analyses showed that age, gender, and race had no clinically meaningful influence on ceritinib exposure.

### **Hepatic impairment**

The effect of hepatic impairment on the single dose pharmacokinetics of ceritinib (750 mg fasted) was evaluated in subjects with mild (Child-Pugh class A; N = 8), moderate (Child-Pugh class B; N = 7), or severe (Child-Pugh class C; N = 7) hepatic impairment and in 8 healthy subjects with normal hepatic function. The geometric mean systemic exposure (AUC<sub>inf</sub>) of ceritinib was increased by 18% and 2% in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function. No dose adjustment is necessary in patients with mild or moderate hepatic impairment (see section DOSAGE REGIMEN AND ADMINISTRATION).

The geometric mean systemic exposure (AUC<sub>inf</sub>) of ceritinib was increased by 66% in subjects with severe hepatic impairment compared to subjects with normal hepatic function. For patients with severe hepatic impairment, reduce the dose of Spebib by approximately one-third rounded to the nearest multiple of the 150 mg dosage strength (see section DOSAGE REGIMEN AND ADMINISTRATION).

### **Renal impairment**

Ceritinib has not been studied in patients with renal impairment. However, based upon available data, ceritinib elimination via the kidney is negligible (1.3% of a single oral administered dose).

Based on a population pharmacokinetic analysis of 345 patients with mild renal impairment (CLcr 60 to <90 mL/min), 82 patients with moderate renal impairment (CLcr 30 to <60 mL/min) and 546 patients with normal renal function ( $\geq$ 90 mL/min), ceritinib exposures were similar in patients with mild and moderate renal impairment and normal renal function, suggesting that no dose adjustment is necessary in patients with mild to moderate renal impairment (see section DOSAGE REGIMEN AND ADMINISTRATION). Patients with severe renal impairment (CLcr <30 mL/min) were not included in the clinical trial.

### **Cardiac electrophysiology**

The potential for QT interval prolongation of ceritinib was assessed in 7 clinical studies with Spebib. Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of ceritinib on the QT interval in 925 patients treated with Spebib 750 mg once daily fasted. A categorical outlier analysis of ECG data demonstrated new QTc >500 msec in 12 patients (1.3%). There were 58 patients (6.3%) with a QTc increase from baseline >60 msec. A central tendency analysis of the QTc data at average steady-state concentrations from a global phase 3 study (Study A2301) demonstrated that the upper bound of the 2-sided 90% CI for QTc was 15.3 msec at ceritinib 750 mg fasted. A pharmacokinetic/ pharmacodynamic analysis suggested that ceritinib causes concentration-dependent increases in QTc (see section WARNINGS AND PRECAUTIONS).

## **CLINICAL STUDIES**

### ***Previously untreated ALK-positive locally advanced or metastatic NSCLC - Randomized Phase 3 Study A2301 (ASCEND-4)***

The efficacy and safety of Spebib for the treatment of locally advanced or metastatic ALK-positive NSCLC patients with and without brain metastasis, who have not received previous systemic treatment anti-cancer therapy (including ALK inhibitor) with the exception of neo-adjuvant or adjuvant therapy, was demonstrated in a global multicenter, randomized, open-label Phase 3 Study A2301.

The primary efficacy endpoint was progression-free survival (PFS), as determined by a Blinded Independent Review Committee (BIRC), according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The key secondary endpoint was Overall Survival (OS). Other secondary endpoints included Overall Response Rate (ORR), Duration of Response (DOR), disease control rate (DCR), and time to response (TTR) determined by BIRC and by Investigators and patient reported outcomes (PROs), including disease-related symptoms, functioning, and health-related quality of life.

Intracranial ORR (OIRR), intracranial DCR (IDCR) and duration of intracranial response (DOIIR) determined by BIRC neuro-radiologist per modified RECIST 1.1 (i.e. up to 5 lesions in the brain) were used to assess the antitumor activity in the brain.

Patients were allowed to continue the assigned study treatment beyond initial progression in case of continued clinical benefit as per the Investigator's opinion. Patients randomized to the chemotherapy arm could crossover to receive ceritinib upon RECIST-defined disease progression by BIRC.

A total of 376 patients were randomized in a 1:1 ratio (stratified by WHO performance status, prior adjuvant/neoadjuvant chemotherapy and presence/absence of brain metastasis at screening) to receive either ceritinib (750 mg once daily, fasted) or chemotherapy (based on Investigator's choice - pemetrexed (500 mg/m<sup>2</sup>) plus cisplatin (75 mg/m<sup>2</sup>) or carboplatin (AUC 5-6), administered every 21 days). Patients who completed 4 cycles of chemotherapy (induction) without progressive disease subsequently received pemetrexed (500 mg/m<sup>2</sup>) as single-agent maintenance therapy every 21 days. One hundred and eighty-nine (189) patients were randomized to ceritinib and one hundred eighty-seven (187) were randomized to chemotherapy.

The overall median age was 54 years (range: 22 to 81 years); 78.5% of patients were younger than 65 years. A total of 57.4% of patients were female. 53.7% of the study population was Caucasians, 42.0%, Asians, 1.6%, Blacks and 2.6% other races. The majority of patients had adenocarcinoma (96.5%) and had either never smoked or were former smokers (92.0%). The Eastern Cooperative Oncology Group (ECOG) performance status was 0/1/2 in 37.0%/56.4%/6.4% of patients respectively, and 32.2% had neurologically stable (symptomatic or not) brain metastasis at baseline. Baseline disease characteristics were well-balanced between the two treatment arms.

The median duration of follow-up was 19.7 months (from randomization to data cut-off date).

The study met its primary objective demonstrating a statistically significant and clinically meaningful improvement in PFS by BIRC with an estimated 45% risk reduction in the ceritinib arm compared to the chemotherapy arm (HR: 0.55 with 95% CI: 0.42, 0.73, p<0.001). The median PFS was 16.6 months (95% CI: 12.6, 27.2) and 8.1 months (95% CI: 5.8, 11.1) for the ceritinib arm and chemotherapy arm, respectively (see Table 3 and Figure 1).

The PFS benefit of ceritinib over chemotherapy was robust and consistent by Investigator assessment and across various subgroups including age, gender, race, smoking class, Eastern Cooperative Oncology Group (ECOG) performance status and disease burden.

Ceritinib also significantly improved BIRC-assessed ORR as compared to chemotherapy with durable response (see Table 3). The overall survival (OS) data was not mature at the time of primary PFS analysis. There were fewer deaths in the ceritinib arm (48 events, 25.4%) than in the chemotherapy arm (59 events, 31.6%), indicating a trend favoring ceritinib. The median OS was not estimable in the ceritinib arm and was 26.2 months (95% CI: 22.8, NE) in the chemotherapy arm. The estimated OS rate (95% CI) at 24 months was 70.6% (62.2, 77.5) and 58.2% (47.6, 67.5) for ceritinib arm and chemotherapy arm, respectively. Eighty-one patients (43.3%) in the chemotherapy arm received subsequent ceritinib as first antineoplastic therapy after study treatment discontinuation.

Efficacy data from Study A2301 are summarized in Table 3, and the Kaplan-Meier curves for PFS and OS are shown in Figure 1 and Figure 2, respectively.

**Table 3 ASCEND-4 (Study A2301) - Efficacy results in patients with previously untreated ALK-positive locally advanced or metastatic NSCLC**

	<b>Ceritinib (N=189)</b>	<b>Chemotherapy (N=187)</b>
<b>Progression-Free Survival (based on BIRC)</b>		
Number of events, n (%)	89 (47.1)	113 (60.4)
Median, months <sup>d</sup> (95% CI)	16.6 (12.6, 27.2)	8.1 (5.8, 11.1)
HR (95% CI) <sup>a</sup>	0.55 (0.42, 0.73)	
p-value <sup>b</sup>	<0.001	
<b>Overall Survival<sup>c</sup></b>		
Number of events, n (%)	48 (25.4)	59 (31.6)
Median, months <sup>d</sup> (95% CI)	NE (29.3, NE)	26.2 (22.8, NE)
OS rate at 24 months <sup>d</sup> , % (95% CI)	70.6 (62.2, 77.5)	58.2 (47.6, 67.5)
HR (95% CI) <sup>a</sup>	0.73 (0.50, 1.08)	
p-value <sup>b</sup>	0.056	
<b>Tumor Response (based on BIRC)</b>		
Objective response rate (95% CI)	72.5% (65.5, 78.7)	26.7% (20.5, 33.7)
<b>Duration of response (based on BIRC)</b>		
Number of responders	137	50
Median, months <sup>d</sup> (95% CI)	23.9 (16.6, NE)	11.1 (7.8, 16.4)
Event-free rate at 18 months <sup>d</sup> , % (95% CI)	59.0 (49.3, 67.4)	30.4 (14.1, 48.6)

HR=hazard ratio; CI=confidence interval; BIRC=Blinded Independent Review Committee; NE=not estimable; CR=complete response; PR=partial response

<sup>a</sup>Based on the Cox proportional hazards stratified analysis.

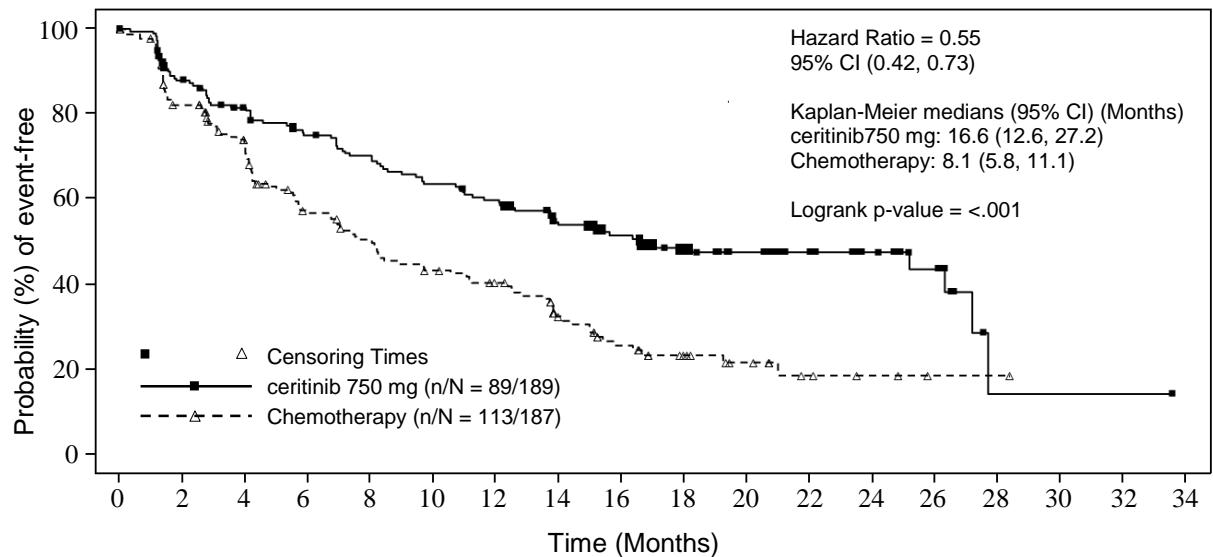
<sup>b</sup>Based on the stratified log-rank test.

<sup>c</sup>OS analysis was not adjusted for the effects of cross over.

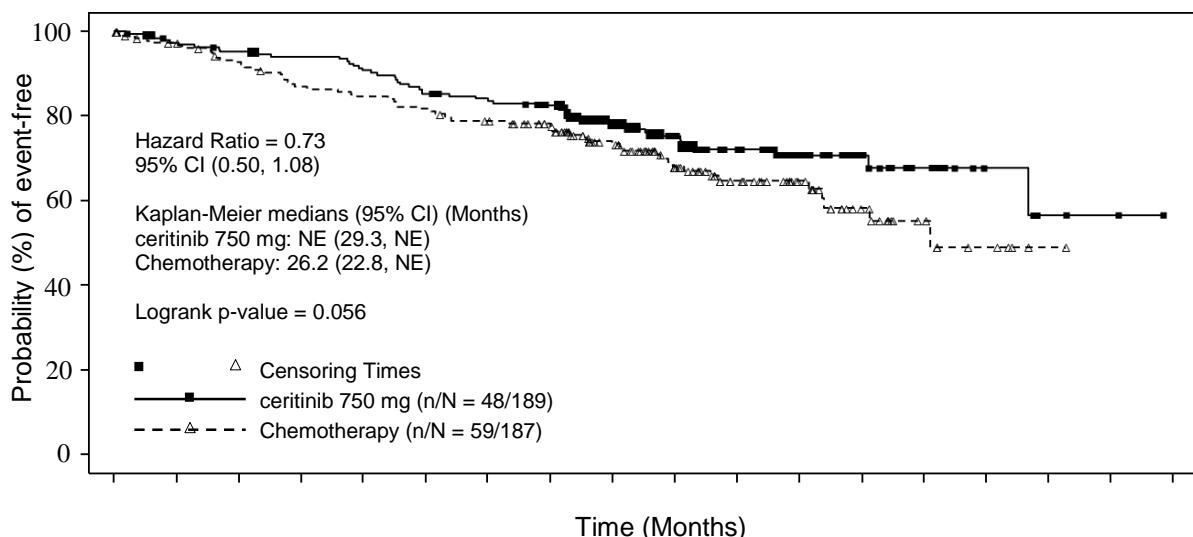
<sup>d</sup>Estimated using the Kaplan-Meier method.

**Figure 1**

**ASCEND-4 (Study A2301) - Kaplan-Meier plot of progression-free survival as assessed by BIRC**



Time (Months)	No. of patients still at risk																	
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
LDK378 750 mg	189	155	139	125	116	105	98	76	59	43	32	23	16	11	1	1	1	0
Chemotherapy	187	136	114	82	71	60	53	35	24	16	11	5	3	1	1	0	0	0

**Figure 2****ASCEND-4 (Study A2301) - Kaplan-Meier plot of overall survival**

Time (Months)	No. of patients still at risk																	
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
LDK378 750	189	180	175	171	165	155	150	138	103	77	56	39	26	18	6	3	2	0
Chemotherapy	187	172	161	150	146	141	134	124	97	69	49	35	19	10	5	1	0	0

Ceritinib significantly prolonged time to deterioration for lung cancer specific symptoms as shown by the composite endpoint of cough, pain and dyspnea in the Lung Cancer Symptom Score (LCSS) (HR = 0.61, 95% CI: 0.41, 0.90) and QLQ-LC13 (HR = 0.48, 95% CI: 0.34, 0.69) instruments compared to chemotherapy. Median time to definitive deterioration for the LC13 composite endpoint (pain, cough, shortness of breath) was 23.6 months (95% CI: 20.7, NE) in the ceritinib arm versus 12.6 months (95% CI: 8.9, 14.9) in the chemotherapy arm.

Patients receiving ceritinib showed significant improvements over chemotherapy in General Quality of Life (LCSS,  $p < 0.001$ ), Global Health Status/QoL (QLQ-C30,  $p < 0.001$ ) as well as in EQ-5D-5L index ( $p < 0.001$ ) and EQ-5D-5L VAS ( $p < 0.05$  from each treatment cycle from 13 until 49). Overall, these results suggest improvements in lung cancer specific symptoms as well as general health status benefits for ALK-positive NSCLC patients treated with ceritinib versus chemotherapy.

In Study A2301, 44 out of 121 patients had active and measurable brain metastasis at baseline and at least one post-baseline brain radiological assessment (22 in the ceritinib arm and 22 patients in the chemotherapy arm). An active brain metastasis is defined as an untreated brain metastasis, new brain metastasis or an existing brain metastasis with documented progression after the end of the brain radiotherapy. These 44 patients were assessed for intracranial response by BIRC neuro-radiologist. The intracranial ORR (OIRR) was higher with ceritinib (72.7%, 95% CI: 49.8, 89.3) as compared to the chemotherapy arm (27.3%, 95% CI: 10.7, 50.2). Among these patients, 59.1% (13/22) in the ceritinib arm and 81.8% (18/22) in the chemotherapy arm did not receive prior radiotherapy to the brain.

The median PFS by BIRC and Investigator using RECIST 1.1 was longer in the ceritinib arm compared to the chemotherapy arm in both subgroups of patients with brain metastases and without brain metastases (based on the extent of cancer CRF, see Table 4).

**Table 4** ASCEND-4 (Study A2301) – PFS with and without brain metastases

	BIRC		Investigator	
	Ceritinib	Chemotherapy	Ceritinib	Chemotherapy
<b>With Brain Metastases</b>	<b>N=59</b>	<b>N=62</b>	<b>N=59</b>	<b>N=62</b>
Progression Free Survival				
Median, months (95% CI)	10.7 (8.1, 16.4)	6.7 (4.1, 10.6)	13.5 (9.0, 16.7)	6.7 (4.2, 10.6)
HR (95% CI)	0.70 (0.44, 1.12)		0.58 (0.36, 0.92)	
<b>Without Brain Metastases</b>	<b>N=130</b>	<b>N=125</b>	<b>N=130</b>	<b>N=125</b>
Progression Free Survival				
Median, months (95% CI)	26.3 (15.4, 27.7)	8.3 (6.0, 13.7)	25.2 (13.9, NE)	8.3 (5.8, 11.1)
HR (95% CI)	0.48 (0.33, 0.69)		0.44 (0.31, 0.63)	

***Previously treated ALK-positive locally advanced or metastatic NSCLC - Randomized Phase 3 Study A2303 (ASCEND-5)***

The efficacy and safety of Spebib for the treatment of locally advanced or metastatic ALK-positive NSCLC patients with and without brain metastasis, who have received previous treatment with crizotinib, was demonstrated in a global multicenter, randomized, open-label Phase 3 Study A2303.

The primary efficacy endpoint was PFS, as determined by BIRC, according to RECIST 1.1. The key secondary endpoint was Overall Survival (OS). Other secondary endpoints included Overall Response Rate (ORR), Duration of Response (DOR), disease control rate (DCR), and time to response (TTR) determined by BIRC and by Investigator, PFS by Investigator and patient reported outcomes (PROs), including disease-related symptoms, functioning, and health-related quality of life.

Intracranial ORR (OIRR), intracranial DCR (IDCR) and duration of intracranial response (DOIIR) determined by BIRC neuro-radiologist per modified RECIST 1.1 (i.e. up to 5 lesions in the brain) were used to assess the antitumor activity in the brain.

Patients were allowed to continue the assigned study treatment beyond initial progression in case of continued clinical benefit as per the Investigator's opinion. Patients randomized to the chemotherapy arm could crossover to receive ceritinib upon RECIST-defined disease progression confirmed by BIRC.

A total of 231 patients with advanced ALK positive NSCLC who have received prior treatment with crizotinib and chemotherapy (one or two regimen including a platinum-based doublet) were included in the analysis. 115 patients were randomized to ceritinib and 116 were randomized to chemotherapy. 73 patients received docetaxel and 40 received pemetrexed. In the ceritinib arm, 115 patients were treated with 750 mg once daily fasted.

Baseline disease characteristics were well-balanced between the two treatment arms. The median age was 54.0 years (range: 28 to 84 years); 77.1% of patients were younger than 65 years. A total of 55.8% of patients were female. 64.5% of the study population were Caucasians, 29.4% Asians, 0.4% Blacks and 2.6% other races. The majority of patients had adenocarcinoma (97.0%) and had either never smoked or were former smokers (96.1%). The ECOG performance status was 0/1/2 in 46.3%/47.6%/6.1% of patients respectively, and 58.0% had brain metastasis at baseline. All patients were treated with prior crizotinib. 198 patients (81.8%) received crizotinib as last treatment. All except one patient received prior chemotherapy (including a platinum doublet) for advanced disease; 11.3% of the patients in the ceritinib arm and 12.1% of the patients in the chemotherapy arm were treated with two prior chemotherapy regimen for advanced disease.

The median duration of follow-up was 16.5 months (from randomization to data cut-off date).

The study met its primary objective demonstrating a statistically significant and clinically meaningful improvement in PFS by BIRC with an estimated 51% risk reduction in the ceritinib arm compared to chemotherapy arm (HR: 0.49 with 95% CI: 0.36, 0.67). The median PFS was 5.4 months (95% CI: 4.1, 6.9) and 1.6 months (95% CI: 1.4, 2.8) for the ceritinib arm and chemotherapy arm, respectively (see Table 5 and Figure 3).

The PFS benefit of ceritinib over chemotherapy was robust and consistent by Investigator assessment and across various subgroups including age, gender, race, smoking class, ECOG performance status, and presence of brain metastases or prior response to crizotinib.

Ceritinib also significantly improved BIRC-assessed ORR as compared to chemotherapy with durable response (see Table 5). The OS data was not mature at the time of primary PFS analysis. In addition, 81 patients (69.8%) in the chemotherapy arm received subsequent ceritinib as first antineoplastic therapy after study treatment discontinuation.

Efficacy data from Study A2303 are summarized in Table 5, and the Kaplan-Meier curves for PFS and OS are shown in Figure 3 and Figure 4, respectively.

**Table 5 ASCEND-5 (Study A2303) – Efficacy result in patients with previously treated ALK-positive locally advanced or metastatic NSCLC**

	<b>Ceritinib (N=115)</b>	<b>Chemotherapy (N=116)</b>
<b>Progression-free survival (based on BIRC)</b>		
Number of events, n (%)	83 (72.2%)	89 (76.7%)
Median, months (95% CI)	5.4 (4.1, 6.9)	1.6 (1.4, 2.8)
HR (95% CI) <sup>a</sup>	0.49 (0.36, 0.67)	
p-value <sup>b</sup>	<0.001	
<b>Overall survival<sup>c</sup></b>		
Number of events, n (%)	48 (41.7%)	50 (43.1%)
Median, months (95% CI)	18.1 (13.4, 23.9)	20.1 (11.9, 25.1)
HR (95% CI) <sup>a</sup>	1.00 (0.67, 1.49)	
p-value <sup>b</sup>	0.496	
<b>Tumor response (based on BIRC)</b>		
Objective response rate (95% CI)	39.1% (30.2, 48.7)	6.9% (3.0, 13.1)
<b>Duration of response</b>		
Number of responders	45	8
Median, months <sup>d</sup> (95% CI)	6.9 (5.4, 8.9)	8.3 (3.5, NE)
Event-free probability estimate at 9 months <sup>d</sup> (95% CI)	31.5% (16.7%, 47.3%)	45.7% (6.9%, 79.5%)

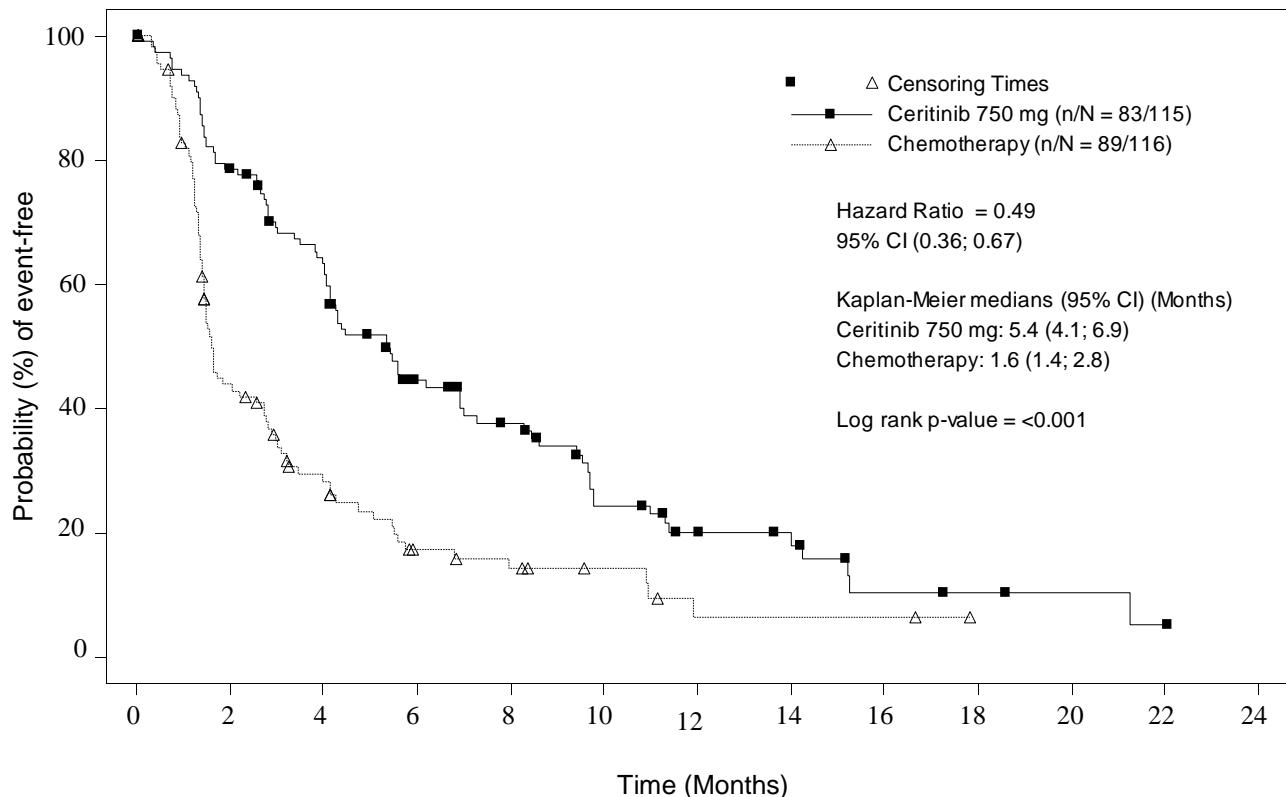
*HR=hazard ratio; CI=confidence interval; BIRC=Blinded Independent Review Committee; NE=not estimable;*

<sup>a</sup> Based on the Cox proportional hazards stratified analysis.

<sup>b</sup> Based on the stratified log-rank test.

<sup>c</sup> OS analysis was not adjusted for the effects of cross over.

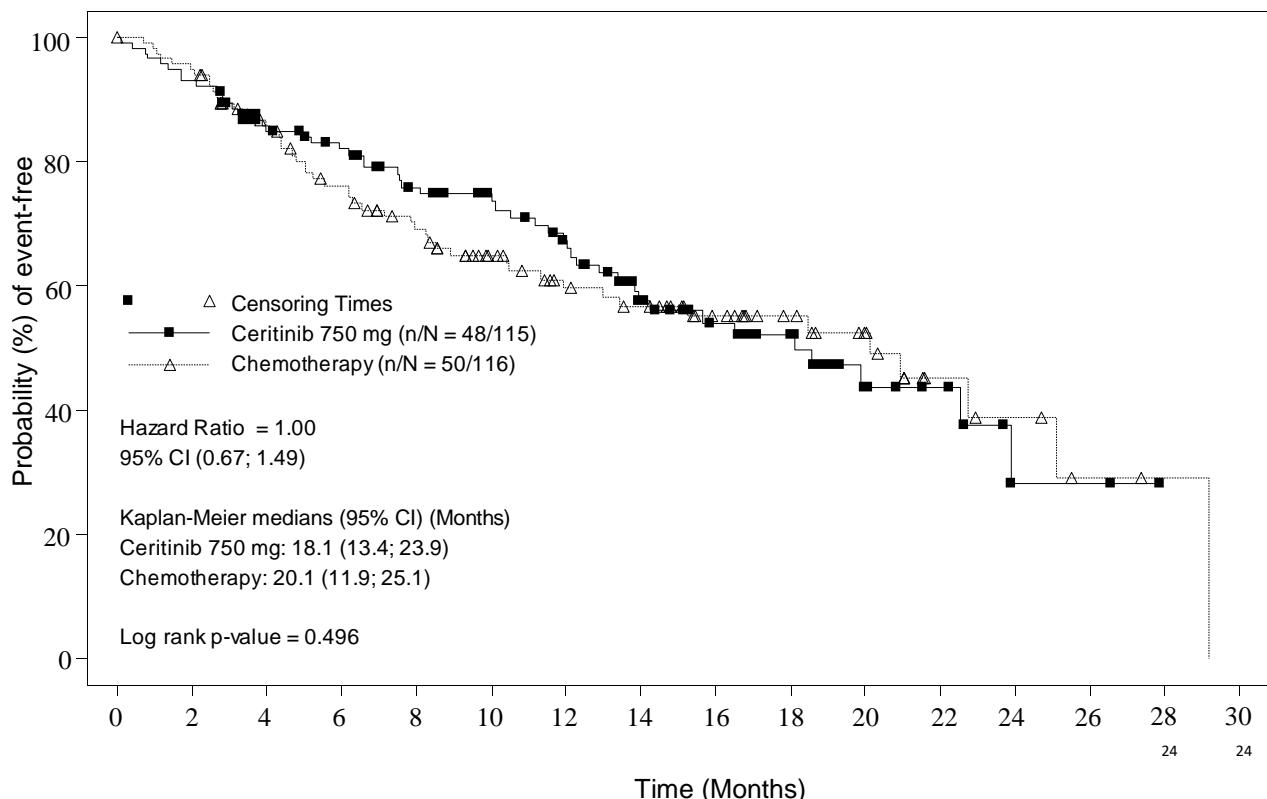
<sup>d</sup> Estimated using the Kaplan-Meier method.

**Figure 3****ASCEND-5 (Study A2303) - Kaplan-Meier plot of progression-free survival as assessed by BIRC**

Time (Months)	No. of patients still at risk												
	0	2	4	6	8	10	12	14	16	18	20	22	24
LDK378 750 mg	115	87	68	40	31	18	12	9	4	3	2	1	0
Chemotherapy	116	45	26	12	9	6	2	2	2	0	0	0	0

Figure 4

ASCEND-5 (Study A2303) - Kaplan-Meier plot of overall survival



Time (Months)	No. of patients still at risk															
	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
LDK378 750 mg	115	107	92	83	71	61	52	37	28	23	13	8	2	2	0	0
Chemotherapy	116	109	91	78	66	53	43	39	29	22	17	7	5	2	1	0

Significant improvements were reported for the majority of lung cancer specific symptoms for Spebib versus chemotherapy (LCSS and QLQ-LC13 scores). Time to deterioration for cough, pain and dyspnea was significantly prolonged for the individual scales ( $p$ -value <0.05) or when combined into a composite score ( $p$ -value <0.001) in the LCSS and LC13 instruments. Median time to definitive deterioration for the LCSS composite endpoint (pain, cough, shortness of breath) was 18 months (95% CI: 13.4, NE) in the ceritinib arm versus 4.4 months (95% CI: 1.6, 8.6) in the chemotherapy arm. Median time to definitive deterioration for the same endpoint in the LC13 instrument was 11.1 months (95% CI 7.1, 14.2) in the ceritinib arm versus 2.1 months (95% CI: 1.0, 5.6) in the chemotherapy arm.

The EQ-5D questionnaire showed a significant overall health status improvement for Spebib in comparison to the chemotherapy.

In Study A2303, 133 patients with baseline brain metastasis (66 patients in the ceritinib arm and 67 patients in the chemotherapy arm) were assessed for intracranial response by BIRC neuro-radiologist. The intracranial ORR (OIRR) in patients with measurable disease in the brain at baseline and at least one post-baseline assessment was higher with ceritinib (35.3%, 95% CI: 14.2, 61.7) compared to chemotherapy (5.0%, 95% CI: 0.1, 24.9).

The median PFS by BIRC and Investigator using RECIST 1.1 was longer in the ceritinib arm compared to the chemotherapy arm in both subgroups of patients with brain metastases and without brain metastases (based on the extent of cancer CRF, see Table 6).

**Table 6** ASCEND-5 (Study A2303) – PFS with and without brain metastases

	BIRC		Investigator	
	Ceritinib	Chemotherapy	Ceritinib	Chemotherapy
<b>With Brain Metastases</b>	<b>N=65</b>	<b>N=69</b>	<b>N=65</b>	<b>N=69</b>
Progression Free Survival				
Median, months (95% CI)	4.4 (3.4, 6.2)	1.5 (1.3, 1.8)	5.4 (3.9, 7.0)	1.5 (1.3, 2.1)
HR (95% CI)		0.54 (0.36, 0.80)		0.45 (0.31, 0.66)
<b>Without Brain Metastases</b>	<b>N=50</b>	<b>N=47</b>	<b>N=50</b>	<b>N=47</b>
Progression Free Survival				
Median, months (95% CI)	8.3 (4.1, 14.0)	2.8 (1.4, 4.1)	8.3 (5.6, 13.4)	2.6 (1.4, 4.2)
HR (95% CI)		0.41 (0.24, 0.69)		0.32 (0.19, 0.54)

**Dose optimization Study A2112 (ASCEND-8)**

The efficacy of Spexib 450 mg with food was evaluated in a multicenter, open-label dose optimization Study A2112 (ASCEND-8). A total of 81 previously untreated patients with ALK-positive locally advanced or metastatic NSCLC were randomized to receive Spexib 450 mg once daily with food (N=41) or Spexib 750 mg once daily under fasted conditions (N=40). ALK-positivity was identified by VENTANA IHC. A key secondary efficacy endpoint was overall response rate (ORR) according to RECIST 1.1 as evaluated by a Blinded Independent Review Committee (BIRC).

The population characteristics across the two arms were: mean age 53 years, age less than 65 (79%), female (57%), Caucasian (54%), Asian (33%), never or former smoker (95%), WHO PS 0 or 1 (93%), adenocarcinoma histology (94%), and metastases to the brain (33%).

Efficacy results from ASCEND-8 are summarized in Table 7 below.

**Table 7** ASCEND-8 (Study A2112) - Efficacy results in patients with previously untreated ALK positive locally advanced or metastatic NSCLC by BIRC

Efficacy Parameter	Spexib 450 mg with food (N=41)	Spexib 750 mg fasted (N=40)
Overall Response Rate (ORR: CR+PR), n (%) (95% CI) <sup>a</sup>	32 (78.0) (62.4, 89.4)	28 (70.0) (53.5, 83.4)

BIRC: Blinded Independent Review Committee; CI: Confidence Interval

CR, PR confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met

Overall response rate determined based on BIRC assessment per RECIST 1.1

<sup>a</sup>Exact binomial 95% confidence interval

**Single-arm studies X2101, A2203 and A2201**

The use of Spexib in the treatment of ALK-positive NSCLC patients was investigated in 3 global, multicenter, open-label, single-arm studies (Study X2101, Study A2203, and Study A2201).

The primary efficacy endpoint for these studies was overall response rate (ORR) by investigator for patients who were treated with a Spexib dose of 750 mg fasted, defined as the proportion of patients with best response of complete response (CR) or partial response (PR) confirmed by repeat assessments performed not less than 4 weeks after the criteria for response was first met. Additional evaluations included duration of response (DOR) and progression-free survival (PFS) by Investigator assessment, and overall survival (OS). Tumor evaluations were performed by the Investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 in Study X2101 and RECIST 1.1 in Studies A2203 and A2201.

**Study X2101** was a global, multicenter, open-label, phase 1 study which included a dose-escalation phase and an expansion phase, at a dose of 750 mg on an empty stomach. All patients enrolled in the study had locally advanced or metastatic malignancy that had progressed despite standard therapy and all patients were previously tested for ALK rearrangement. Patients with controlled or asymptomatic brain metastases were eligible for the study. Prior ALK inhibitor therapy was permitted. Two-hundred and ninety of the 304 patients enrolled in the study were ALK-positive NSCLC patients. A total of 246 ALK-positive NSCLC patients were enrolled who were treated at a Spebib dose of 750 mg fasted: 163 who had received prior treatment with an ALK inhibitor and 83 who were ALK inhibitor naïve.

Across the 246 ALK-positive NSCLC patients treated at a dose of 750 mg fasted in the study, the median age was 53 years (range: 22 to 80 years); 84.1% of patients were younger than 65 years. A total of 53.7% of patients were female. Caucasians comprised 63.4% of the study population, Asians 33.3%, Blacks 1.6%, and other races 1.6%. The vast majority of patients had adenocarcinoma (92.7%) and were either never or former smokers (97.6%). More than two-thirds (67.5%) of the patients were treated with 2 or more regimens prior to enrollment into the study, 26.0% with 1 prior regimen, and 6.5% with 0 prior regimens.

Both **Study A2203** and **Study A2201** were global, multicenter, open-label, single-arm, phase 2 studies designed to evaluate the efficacy and safety of 750 mg ceritinib fasted in patients with locally advanced or metastatic ALK-positive NSCLC. Study A2203 enrolled 124 crizotinib-naïve patients who were either chemotherapy-naïve or who had been previously treated with up to 3 lines of cytotoxic chemotherapy. Study **A2201** enrolled 140 patients who had been previously treated with 1 to 3 prior lines of cytotoxic chemotherapy followed by treatment with crizotinib, and then progressed on crizotinib.

In Study A2203, 124 patients were treated at a dose of 750 mg fasted. The median age was 56 years (range: 27 to 82 years); 75.8% of patients were younger than 65 years. A total of 59.7% of patients were female. Asians comprised 59.7% of the study population, Caucasians 38.7%, Blacks 0.8%, and other races 0.8%. The vast majority of patients had adenocarcinoma (96.8%). All patients, except 2 who were naïve to anti-cancer treatment, were treated with prior chemotherapy. 54 (43.5%) patients were treated with 1 regimen and 68 (54.8%) were treated with 2 or more regimens prior to enrollment into this study. All patients were ALK inhibitor naïve.

In Study A2201, 140 patients were treated at a dose of 750 mg fasted. The median age was 51 years (range: 29 to 80 years); 87.1% of patients were younger than 65 years. A total of 50.0% of patients were female. Caucasians comprised 60.0% of the study population, Asians 37.9% and other races 2.1%. The vast majority of patients had adenocarcinoma (92.1%). All patients were treated with 2 or more regimens prior to enrollment into the study. All patients had received prior treatment with an ALK inhibitor.

**Main efficacy results from Studies X2101, A2203 and A2201**

In Study A2203, the median OS was 51.3 months (95% CI: 42.7, 55.3) at the final analysis (data cut-off date: 22-Jan-2018) and a high proportion of patients were censored (68 patients; 54.8%). The OS rate was 67.3% (95% CI: 58.1, 75.0) at 30 months.

The main efficacy data for all 3 studies are summarized in Table 8 for ALK-positive NSCLC patients who are ALK inhibitor naïve and in Table 9 for ALK-positive NSCLC patients with prior ALK inhibitor treatment. Patients responded to Spexib regardless of whether they received a prior ALK inhibitor as shown in Tables 8 and 9. With longer follow-up (median duration > two years), patients continued to demonstrate a clinical response to Spexib.

**Table 8 Overview of efficacy data in ALK-positive NSCLC patients who are ALK inhibitor naïve per Investigator assessment**

	Study X2101 ceritinib 750 mg N=83		Study A2203 ceritinib 750 mg N=124	
<b>Duration of follow-up</b>				
Median (months) (min – max)	12.5* (0.4 – 22.2)	39.8** (33.1 – 52.5)	9.3** (5.6 – 17.2)	25.9** (22.2 – 33.8)
<b>Overall response rate (CR + PR), n (%)</b>	60 (72.3) (61.4, 81.6)	61 (73.5) (62.7, 82.6)	79 (63.7) (54.6, 72.2)	84 (67.7) (58.8, 75.9)
<b>Duration of response***</b>				
Median (months) (95% CI)	17.0 (11.3, NE)	14.2 (11.3, 22.1)	9.3 (9.1, NE)	22.1 (14.8, NE)
% Event-free probability estimate (95% CI) at 18 months	37.6 (9.7, 66.3)	42.8 (29.9, 55.1)	NE	55.7 (44.2, 65.7)
<b>Progression-free survival</b>				
Median (months) (95% CI)	18.4 (11.1, NE)	15.2 (12.1, 19.5)	11.1 (9.3, NE)	16.6 (11.0, 22.1)
% Event-free probability estimate (95% CI) at 18 months	50.6 (36.1, 63.5)	44.2 (32.8, 55.1)	NE	49.1 (39.7, 57.9)
<b>Overall survival</b>				
Median (months) (95% CI)	NE (19.6, NE)	39.1 (32.9, NE)	NE (NE, NE)	NE (NE, NE)
% Event-free probability estimate (95% CI) at 18 months	79.6 (66.5, 88.0)	75.2 (63.8, 83.5)	NE	73.4 (64.6, 80.4)
<b>Data cut-off date</b>	14-Apr-2014	3-May-2016	27-Jun-2014	15-Nov-2015

NE = not estimable

Study X2101: Responses assessed by Investigator; Overall response rate determined per RECIST 1.0

Study A2203: Responses assessed by Investigator; Overall response rate determined per RECIST 1.1

CR, PR confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met

\*From start date of study treatment to date of death or censoring

\*\*From start date of study treatment to cut-off date

\*\*\*Includes only patients with confirmed CR, PR

**Table 9** Overview of efficacy data in ALK-positive NSCLC patients with prior ALK inhibitor treatment per Investigator assessment

	Study X2101 ceritinib 750 mg N=163	Study A2201 ceritinib 750 mg N=140		
<b>Duration of follow-up</b>				
Median (months) (min – max)	10.2* (0.1 – 24.1)	40.0** (33.1 – 52.7)	8.3** (5.6 – 14.8)	33.4** (30.6 – 39.8)
<b>Overall response rate (CR + PR), n (%)</b>	92 (56.4) (48.5, 64.2)	92 (56.4) (48.5, 64.2)	52 (37.1) (29.1, 45.7)	57 (40.7) (32.5, 49.3)
<b>Duration of response***</b>				
Median (months) (95% CI)	8.3 (6.8, 9.7)	8.3 (6.8, 9.7)	9.2 (5.6, NE) <sup>#</sup>	10.6 (7.4, 14.7)
<b>Progression-free survival</b>				
Median (months) (95% CI)	6.9 (5.6, 8.7)	6.9 (5.6, 8.5)	5.7 (5.3, 7.4)	5.8 (5.4, 7.6)
<b>Overall survival</b>				
Median (months) (95% CI)	16.7 (14.8, NE) <sup>##</sup>	20.3 (15.2, 24.3)	14.0 (10.3, 14.0)	15.6 (13.6, 24.2)
<b>Data cut-off date</b>	14-Apr-2014	3-May-2016	26-Feb-2014	29-Mar-2016

NE = not estimable

Study X2101: Responses assessed by Investigator; Overall response rate determined per RECIST 1.0

Study A2201: Responses assessed by Investigator; Overall response rate determined per RECIST 1.1

CR, PR confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met

\*From start date of study treatment to date of death or censoring

\*\*From start date of study treatment to cut-off date

\*\*\*Includes only patients with confirmed CR, PR

<sup>#</sup>DOR rate at 8 months is 51.3% (32.7, 67.1)

<sup>##</sup>OS rate at 18 months is 47.5% (36.4, 57.8)

The majority of patients treated with Spexib, who had measurable disease at baseline and at least one valid post-baseline assessment, had a reduction in measurable lesions as best percentage change from baseline based on Investigator assessment, i.e. 207 (90.79%), 94 (75.81%) and 108 (94.74%) in Study X2101, A2201 and A2203 respectively.

#### Patients with brain metastases

In the analysis of Studies X2101, A2203, and A2201 at an early cut off date, brain metastases were seen in 50.0%, 40.3%, and 71.4% of patients, respectively.

The main efficacy data for patients with brain metastases at baseline for all 3 studies are summarized in Table 10.

**Table 10****Overview of efficacy data in ALK-positive NSCLC patients with brain metastases at baseline**

	Patients who are ALK inhibitor naïve		Patients with prior ALK inhibitor treatment	
	Study X2101 ceritinib 750 mg N=26	Study A2203 ceritinib 750 mg N=50	Study X2101 ceritinib 750 mg N=98	Study A2201 ceritinib 750 mg N=100
<b>Overall response rate (CR + PR), n (%)</b>	19 (73.1)	29 (58.0)	50 (51.0)	33 (33.0)
(95% CI)	(52.2, 88.4)	(43.2, 71.8)	(40.7, 61.3)	(23.9, 43.1)
<b>Duration of response*</b>				
Median (months) (95% CI)	12.6 (5.5, NE)	9.1 (7.5, NE)	6.9 (5.4, 8.3)	6.1 (5.4, NE)
<b>Progression-free survival</b>				
Median (months) (95% CI)	9.7 (4.6, NE)	10.8 (7.3, NE)	6.9 (4.9, 8.4)	5.4 (4.7, 6.4)
<b>Data cut-off date</b>	14-Apr-2014	27-Jun-2014	14-Apr-2014	26-Feb-2014

*NE = not estimable*  
*Study X2101: Responses assessed by Investigator; Overall response rate determined per RECIST 1.0*  
*Studies A2203 and A2201: Responses assessed by Investigator; Overall response rate determined per RECIST 1.1*  
*CR, PR confirmed by repeat assessments performed not less than 4 weeks after response criteria were first met*  
*\*Includes only patients with confirmed CR, PR*

### Intracranial response

In Study X2101, there were 14 ALK-positive NSCLC patients with investigator-assessed measurable brain metastases at baseline in the 750 mg dose group. The overall intracranial response rate (OIRR) at the cut-off date 14-Apr-2014 as assessed by the Investigator was 50.0% (95% CI: 23.0, 77.0), including 2 patients having a CR in the brain and 5 patients with a confirmed PR in the brain; in addition, 3 patients had stable disease (SD).

In Study A2203, 10 out of the 124 patients with ALK-positive NSCLC had brain metastases at baseline considered to be target lesions by the Investigator. In these patients, the OIRR at the cut-off date 27-Jun-2014 based on Investigator assessment was 20.0% (95% CI: 2.5, 55.6), including 2 patients with a confirmed PR in the brain.

In Study A2201, 20 out of the 140 patients with ALK-positive NSCLC had brain metastases at baseline considered to be target lesions by the Investigator. In these patients, the OIRR at the cut-off date 26-Feb-2014 based on Investigator assessment was 35.0% (95% CI: 15.4, 59.2), including 2 patients with a confirmed CR in the brain and 5 patients with a confirmed PR in the brain.

### Intracranial response without prior irradiation

In addition, for ALK-positive NSCLC patients with measurable brain lesions at baseline that had not been irradiated, Spexib induced responses in the brain that matched or exceeded the systemic tumor responses in the majority of ALK-positive NSCLC patients previously treated with an ALK inhibitor and in ALK inhibitor naïve patients.

In Study X2101, 41 ALK-positive NSCLC patients were enrolled with brain metastases that were not irradiated (30 previously treated with an ALK inhibitor and 11 ALK inhibitor naïve), 4 of whom had measurable brain lesions at baseline (3 previously treated with an ALK inhibitor and 1 ALK inhibitor naïve). At the cut-off date 14-Apr-2014, all 4 of the patients (100%) with measurable brain lesions at baseline that had not been irradiated had responses in the brain that matched or exceeded the systemic tumor responses including 2 complete brain metastases responses (1 for a patient previously treated with an ALK inhibitor and 1 for an ALK inhibitor naïve patient). In addition to the 2 CRs, there was 1 PR and 1 SD.

In Study A2203, 23 ALK-positive NSCLC patients were enrolled with brain metastases that were not irradiated, 6 of whom had measurable brain lesions at baseline. At the cut-off date 27-Jun-2014, all 6 of the patients (100%) had responses in the brain that matched the systemic tumor responses. There were 2 PRs, 3 SDs, and 1 "Unknown".

In Study A2201, 28 ALK-positive NSCLC patients were enrolled with brain metastases that were not irradiated, 6 of whom had measurable brain lesions at baseline. At the cut-off date 26-Feb-2014, 4 of the 6 patients (66.7%) had responses in the brain that matched or exceeded the systemic tumor responses including 2 complete brain metastases responses. In addition to the 2 CRs, there were 2 PRs and 2 SDs.

## NON-CLINICAL SAFETY DATA

### Safety pharmacology and repeat dose toxicity

Safety pharmacology studies indicate that ceritinib is unlikely to interfere with vital functions of the respiratory and central nervous systems. *In vitro* data show that the IC<sub>50</sub> for the inhibitory effect of ceritinib on the hERG potassium channel was 0.4 micromolar at 33°C to 35°C (near body temperature). An *in vivo* telemetry study in monkeys showed a modest QT prolongation in 1 of 4 animals after receiving the highest dose of ceritinib. ECG studies in monkeys after 4- or 13-weeks of dosing with ceritinib have not shown QT prolongation or abnormal ECGs.

The principal toxicity related to ceritinib administration in rats and monkeys was inflammation of the extra-hepatic bile ducts accompanied by increased neutrophil counts in the peripheral blood. Mixed cell/neutrophilic inflammation of the extra-hepatic ducts extended to the pancreas and/or duodenum at higher doses. GI toxicity was observed in both species characterized by body weight loss, decreased food consumption, emesis (monkey), diarrhea, and at high doses, by histopathologic lesions including erosion, mucosal inflammation, and foamy macrophages in the duodenal crypts and submucosa. Liver was also affected in both species, but only at the highest dose levels studied, and included minimal increases in liver transaminases in a few animals, and vacuolation of the intra-hepatic bile duct epithelium. Alveolar foamy macrophages (confirmed phospholipidosis) were seen in the lungs of rats, but not in monkeys, and the lymph nodes of rats and monkeys had macrophage aggregates. Target organ effects showed partial to complete recovery.

### Carcinogenicity and mutagenicity

Carcinogenicity studies have not been performed with ceritinib.

The Ames assay for ceritinib indicated it was not a potential mutagen, and the chromosomal aberration assay in cultured human peripheral blood lymphocytes did not indicate the potential to cause structural chromosomal aberrations. The micronucleus test using cultured human peripheral blood lymphocytes was negative. An *in vivo* rat micronucleus test revealed no adverse chromosomal effects on the bone marrow at any dose level after oral dosing in the rat.

### Fertility and Reproductive toxicity

For information on fertility and reproductive toxicity, see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

## STORAGE

### Special precautions for storage

See folding box.

Spexib should not be used after the date marked "EXPIRY" on the pack.

Spexib must be kept out of the reach and sight of children.

### Instructions for use and handling

There are no special requirements for use or handling of this product.

### Manufacturer:

See folding box.

Information issued: India pack insert dtd 22 Jan 19 based on International Package Leaflet (IPL) dtd 26 Nov 18.  
TM = Trademark of Novartis AG, Basle, Switzerland.

**For the use only of a Registered Medical Practitioner or a Hospital or Laboratory**

**This package insert is continually updated; please read carefully when using a new pack**

## **Enoxaparin Sodium Injection I.P.**

**Pre-Filled syringe**

**Low Molecular Weight Heparin**

**Clexane®**

**Clexane® 20mg/0.2ml**

**Clexane® 40mg/0.4ml**

**Clexane® 60mg/0.6ml**

**Clexane® 80mg/0.8ml**

### **Composition**

Per prefilled syringe of	20 mg	40 mg	60 mg	80 mg
Enoxaparin Sodium I.P.	20 mg	40 mg	60 mg	80 mg
Water for injection I.P. to	0.2 ml	0.4 ml	0.6 ml	0.8 ml

### **Therapeutic or Pharmacological Class**

Antithrombotic Agents. Heparin group.

ATC code: B01A B05 (Antithrombotic Agents; Heparin group)

### **Pharmaceutical Form(s)**

Sterile pyrogen-free solution for injections.

Contained in ready-to-use pre-filled syringes with safety device.

### **Indications**

- Prophylaxis of venous thrombo-embolic disease in patients undergoing, an orthopedic or general surgery procedure, including cancer surgery, with a moderate or high risk of thromboembolism.
- Prophylaxis of venous thrombo-embolism in medical patients bedridden due to acute illnesses including cardiac insufficiency, respiratory failure, severe infections, rheumatic diseases.
- Treatment of deep vein thrombosis with or without pulmonary embolism.
- Prevention of thrombus formation in extra corporeal circulation during hemodialysis.
- Treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin.
- Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI)

### **Dosage and Method of Administration**

#### **General**

##### **• Prophylaxis of venous thrombosis in surgical patients:**

Duration and dose of Clexane therapy are based upon patient risk. The thromboembolic risk for individual patient can be estimated using validated risk stratification models.

In patients with a moderate risk of thrombo-embolism, the recommended dose of enoxaparin sodium is 20mg or 40mg once daily by subcutaneous injection. In general surgery, the first injection should be given 2 hours before the surgical procedure.

Enoxaparin sodium treatment is usually prescribed for an average period of 7 to 10 days. A longer treatment duration may be appropriate in some patients and enoxaparin sodium should be continued for as long as there is a risk of venous thromboembolism and until the patient is ambulatory.

In patients with a high risk of thrombo-embolism, the recommended dose of enoxaparin sodium given by subcutaneous injection, is 40 mg once daily, initiated 12 hours prior to surgery or 30mg twice daily, initiated 12 to 24 hours after surgery.

- For patients who undergo major orthopedic surgery with a high venous thromboembolism risk, a thromboprophylaxis up to 5 weeks is recommended.

- For patients who undergo cancer surgery with a high venous thromboembolism risk, a thromboprophylaxis up to 4 weeks is recommended.

For special recommendations concerning dosing intervals for spinal/epidural anaesthesia and percutaneous coronary revascularisation procedures: (see Warnings).

**• Prophylaxis of venous thromboembolism in medical patients:**

The recommended dose of enoxaparin sodium is 40 mg once daily by subcutaneous injection. Treatment with enoxaparin sodium is prescribed for a minimum of 6 days and continued until the return to full ambulation, for a maximum of 14 days.

**• Treatment of deep vein thrombosis with or without pulmonary embolism:**

Enoxaparin sodium can be administered subcutaneously either as a single injection of 1.5 mg/kg or as twice daily injections of 1 mg/kg. In patients with complicated thromboembolic disorders, a dose of 1mg/kg administered twice daily is recommended.

Enoxaparin sodium treatment is usually prescribed for an average period of 10 days. Oral anticoagulant therapy should be initiated when appropriate and enoxaparin sodium treatment should be continued until a therapeutic anticoagulant effect has been achieved (International Normalisation Ratio 2 to 3).

**• Prevention of extra corporeal thrombus during hemodialysis:**

The recommended dose is 1mg/ kg of enoxaparin sodium.

For patients with a high risk of hemorrhage, the dose should be reduced to 0.5 mg/kg for double vascular access or 0.75 mg/kg for single vascular access.

During hemodialysis enoxaparin sodium should be introduced into the arterial line of the circuit at the beginning of the dialysis session. The effect of this dose is usually sufficient for a 4-hour session; however, if fibrin rings are found, for example after a longer than normal session, a further dose of 0.5 to 1 mg/kg may be given.

**• Treatment of unstable angina and non-Q-wave myocardial infarction:**

The recommended dose of enoxaparin sodium is 1 mg/kg every 12 hours by subcutaneous injection, administered concurrently with oral aspirin (100 to 325 mg once daily).

Treatment with enoxaparin sodium in these patients should be prescribed for a minimum of 2 days and continued until clinical stabilization. The usual duration of treatment is 2 to 8 days.

**• Treatment of acute ST-segment Elevation Myocardial Infarction:**

The recommended dose of enoxaparin sodium is a single IV bolus of 30 mg plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC every 12 hours (max 100 mg for each of the first two SC doses only, followed by 1 mg/kg SC dosing for the remaining doses). For dosage in patients  $\geq$  75 years of age, ( see section Elderly).

When administered in conjunction with a thrombolytic (fibrin specific or non-fibrin specific) enoxaparin sodium should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. All patients should receive acetylsalicylic acid (ASA) as soon as they are identified as having STEMI and maintained under (75 to 325 mg once daily) unless contraindicated.

The recommended duration of enoxaparin sodium treatment is 8 days or until hospital discharge, whichever comes first.

For patients managed with Percutaneous Coronary Intervention (PCI): If the last enoxaparin sodium SC administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last SC administration was given more than 8 hours before balloon inflation, an IV bolus of 0.3 mg/kg of enoxaparin sodium should be administered

**Special populations**

**Children**

The safety and efficacy of enoxaparin sodium in children has not been established.

**Elderly**

For treatment of acute ST-segment Elevation Myocardial Infarction in elderly patients  $\geq$  75 years of age, do not use an initial IV bolus. Initiate dosing with 0.75 mg/kg SC every 12 hours (maximum 75 mg for each of the first two SC doses only, followed by 0.75 mg/kg SC dosing for the remaining doses)

For other indications, no dose reduction is necessary in the elderly, unless kidney function is impaired.

#### **Hepatic impairment**

In the absence of clinical studies, caution should be used in hepatically impaired patients.

#### **Renal impairment**

- **Severe renal impairment:**

A dosage adjustment is required for patients with severe renal impairment (creatinine clearance < 30 ml/min), according to the following tables, since enoxaparin sodium exposure is significantly increased in this patient population.

**The following dosage adjustments are recommended for therapeutic dosage ranges:**

Standard Dosing	Severe renal impairment
1 mg/kg SC twice daily	1 mg/kg SC once daily
1.5 mg/kg SC once daily	1 mg/kg SC once daily
For treatment of acute STEMI in patients < 75 years of age	
30mg single IV bolus plus a 1mg/kg SC dose followed by 1mg/kg SC twice daily (Max 100mg for each of the first two SC doses)	30mg single IV bolus plus a 1mg/kg SC dose followed by 1mg/kg SC once daily (Max 100mg for first SC dose only)
For treatment of acute STEMI in elderly patients ≥ 75 years of age	
0.75 mg/kg SC twice daily without initial bolus (Max 75mg for each of the first two SC doses)	1 mg/kg SC once daily without initial bolus (Max 100mg for first SC dose only)

**The following dosage adjustments are recommended for prophylactic dosage ranges:**

Standard Dosing	Severe renal impairment
40 mg SC once daily	20 mg SC once daily
20 mg SC once daily	20 mg SC once daily

The recommended dosage adjustments do not apply to the hemodialysis indication.

- **Moderate and mild renal impairment:** Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment, careful clinical monitoring is advised.

#### **Spinal/epidural anesthesia**

- For patients receiving spinal/epidural anesthesia see section “Warnings” Spinal/epidural anesthesia.

#### **Administration**

**Subcutaneous injection:** Enoxaparin sodium is administered by subcutaneous injection for the prevention of venous thromboembolic disease, treatment of deep vein thrombosis, treatment of unstable angina and non-Q-wave myocardial infarction and treatment of acute ST segment Elevation Myocardial Infarction.

**IV bolus injection:** For acute ST-segment Elevation Myocardial Infarction, treatment is to be initiated with a single IV bolus injection immediately followed by a subcutaneous injection

**Arterial line injection:** It is administered through the arterial line of a dialysis circuit for the prevention of thrombus formation in the extra-corporeal circulation during haemodialysis. It must not be administered by the intramuscular route.

The prefilled disposable syringe is ready for immediate use. The use of a tuberculin syringe or equivalent is recommended when using multiple-dose vials to assure withdrawal of the appropriate volume of drug

**Subcutaneous injection technique:** Injection should be made preferably when the patient is lying down. Enoxaparin sodium is administered by deep subcutaneous injection. Do not expel the air bubble from the syringe before the injection to avoid the loss of drug when using the 20 and 40 mg prefilled syringes. The administration should be alternated between the left and right anterolateral or posterolateral abdominal wall.

The whole length of the needle should be introduced vertically into a skin fold gently held between the thumb and index finger. The skin fold should not be released until the injection is complete. Do not rub the injection site after administration (see Instructions for use).

**Intravenous (Bolus) Injection Technique (for acute STEMI indication only):**

Enoxaparin sodium should be administered through an intravenous line. It should not be mixed or co-administered with other medications. To avoid the possible mixture of enoxaparin sodium with other drugs, the intravenous access chosen should be flushed with a sufficient amount of saline or dextrose solution prior to and following the intravenous bolus administration of enoxaparin sodium to clear the port of drug. Enoxaparin sodium may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.

**• Initial 30-mg bolus**

For the initial 30 mg bolus, using an enoxaparin sodium graduated prefilled syringe, expel the excessive volume to retain only 30 mg (0.3ml) in the syringe. The 30 mg dose can then be directly injected into the intravenous line.

**• Additional bolus for PCI when last SC administration was given more than 8 hours before balloon inflation**

For patients being managed with Percutaneous Coronary Intervention (PCI), an additional IV bolus of 0.3 mg/kg is to be administered if last SC administration was given more than 8 hours before balloon inflation (see Dosage and Administration: Treatment of acute STEMI).

In order to assure the accuracy of the small volume to be injected, it is recommended to dilute the drug to 3 mg/ml.

To obtain a 3-mg/ml solution, using a 60-mg enoxaparin sodium prefilled syringe, it is recommended to use a 50-ml infusion bag (i.e. using either normal saline solution (0.9%) or 5% dextrose in water) as follows:

Withdraw 30 ml from the infusion bag with a syringe and discard the liquid. Inject the complete contents of the 60-mg enoxaparin sodium prefilled syringe into the 20 ml remaining in the bag. Gently mix the contents of the bag. Withdraw the required volume of diluted solution with a syringe for administration into the intravenous line.

After dilution is completed, the volume to be injected can be calculated using the following formula [Volume of diluted solution (ml) = Patient weight (kg) x 0.1] or using the table below. It is recommended to prepare the dilution immediately before use.

**Volume to be injected through intravenous line after dilution is completed**

Weight [Kg]	Required dose (0.3 mg/kg) [mg]	Volume to inject when diluted to a final concentration of 3 mg/ml [ml]
45	13.5	4.5
50	15	5
55	16.5	5.5
60	18	6
65	19.5	6.5
70	21	7
75	22.5	7.5
80	24	8
85	25.5	8.5
90	27	9
95	28.5	9.5
100	30	10

**Contraindications**

Hypersensitivity to enoxaparin sodium, heparin or its derivatives including other Low Molecular Weight Heparins.

History of immune mediated heparin-induced thrombocytopenia (HIT) within the past 100 days or in the presence of circulating antibodies.

Active major bleeding and conditions with a high risk of uncontrolled hemorrhage, including recent hemorrhagic stroke.

## Warnings

### • General

Low Molecular Weight Heparins should not be used interchangeably since they differ in their manufacturing process, molecular weights, specific anti-Xa activities, units and dosage. This results in differences in pharmacokinetics and associated biological activities (e.g. anti-thrombin activity, and platelet interactions). Special attention and compliance with the instructions for use specific to each proprietary medicinal product are therefore required.

### • Spinal/Epidural Anesthesia

There have been cases of neuraxial haematomas reported with the concurrent use of enoxaparin sodium and spinal/epidural anaesthesia resulting in long term or permanent paralysis. These events are rare with enoxaparin sodium dosage regimens 40 mg once daily or lower. The risk is greater with higher enoxaparin sodium dosage regimens, use of post-operative indwelling catheters or the concomitant use of additional drugs affecting haemostasis such as NSAIDs (see Interactions with other medicinal products or other forms of interaction). The risk also appears to be increased by traumatic or repeated neuraxial puncture or repeated neuraxial puncture or in patients with a history of spinal surgery or spinal deformity.

To reduce the potential risk of bleeding associated with the concurrent use of enoxaparin sodium and epidural or spinal anaesthesia/analgesia, the pharmacokinetic profile of the drug should be considered (See Section Pharmacokinetics). Placement and removal of the catheter is best performed when the anticoagulant effect of enoxaparin is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.

Placement or removal of a catheter should be delayed for atleast 12 hours after administration of lower doses (20 mg once daily, 30 mg once or twice daily or 40 mg once daily) of enoxaparin, and at least 24 hours after the administration of higher doses (0.75 mg/kg twice daily, 1 mg/kg twice daily, or 1.5 mg/kg once daily) of enoxaparin. Anti-Xa levels are still detectable at these time points, and these delays are not a guarantee that neuraxial haematoma will be avoided. Patients receiving the 0.75 mg/kg twice-daily dose or the 1 mg/kg twice-daily dose should not receive the second enoxaparin dose in the twice-daily regimen to allow a longer delay before catheter placement or removal. Likewise, although a specific recommendation for timing of a subsequent enoxaparin dose after catheter removal cannot be made, consider delaying this next dose for at least four hours, based on a benefit-risk assessment considering both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors. For patients with creatinine clearance <30ml/minute, additional considerations are necessary because elimination of enoxaparin is more prolonged; consider doubling the timing of removal of a catheter, at least 24 hours for the lower prescribed dose of enoxaparin (30 mg once daily) and at least 48 hours for the higher dose (1 mg/kg/day).

Should the physician decide to administer anticoagulation in the context of epidural/spinal anesthesia or lumbar puncture, frequent monitoring must be exercised to detect any signs and symptoms of neurological impairment such as midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), bowel and/or bladder dysfunction. Patients should be instructed to inform their physician immediately if they experience any of the above signs or symptoms. If signs or symptoms of spinal haematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated.

### • Heparin-induced thrombocytopenia

Use of enoxaparin sodium in patients with a history of immune mediated HIT within the past 100 days or in the presence of circulating antibodies is contraindicated (see section Contraindications). Circulating antibodies may persist several years.

**Enoxaparin sodium is to be used with extreme caution in patients with a history (more than 100 days) of heparin-induced thrombocytopenia without circulating antibodies. The decision to use enoxaparin sodium in such a case must be made only after a careful benefit risk assessment and after non-heparin alternative treatments are considered.**

### • Percutaneous coronary revascularisation procedures

To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina and non-Q-wave myocardial infarction and acute ST- segment myocardial infarction, adhere precisely to the intervals recommended between Clexane® Injection doses. It is important to achieve hemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be removed immediately. If a manual compression method is used, sheath should be removed 6 hours after the last IV/SC enoxaparin sodium injection. If the treatment with enoxaparin sodium is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation.

- **Pregnant women with mechanical prosthetic heart valves**

The use of Clexane® Injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. There have been isolated post marketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see Precautions: Mechanical prosthetic heart valves).

- **Laboratory tests**

At doses used for prophylaxis of venous thromboembolism, enoxaparin sodium does not influence bleeding time and global blood coagulation tests significantly, nor does it affect platelet aggregation or binding of fibrinogen to platelets. At higher doses, increases in aPTT (activated partial thromboplastin time) and ACT (activated clotting time) may occur. Increases in aPTT and ACT are not linearly correlated with increasing enoxaparin sodium antithrombotic activity and therefore are unsuitable and unreliable for monitoring enoxaparin sodium activity.

#### **Precautions**

- Do not administer by the intramuscular route.
- Hemorrhage: As with other anticoagulants, bleeding may occur at any site (see Adverse Reactions section).
- If bleeding occurs, the origin of the hemorrhage should be investigated and appropriate treatment instituted.
- Enoxaparin sodium, as with any other anticoagulant therapy, should be used with caution in conditions with increased potential for bleeding, such as:
  - impaired hemostasis,
  - history of peptic ulcer,
  - recent ischemic stroke,
  - uncontrolled severe arterial hypertension,
  - diabetic retinopathy,
  - recent neuro- or ophthalmologic surgery,
  - concomitant use of medications affecting hemostasis (see Interactions section).
- Mechanical prosthetic heart valves: The use of Clexane® Injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Confounding factors, including underlying disease and insufficient clinical data, limit the evaluation of these cases. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal death. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism (see Warnings: Pregnant women with mechanical prosthetic heart valves).
- Haemorrhage in the elderly: No increased bleeding tendency is observed in the elderly with the prophylactic dosage ranges. Elderly patients (especially patients eighty years of age and older) may be at an increased risk for bleeding complications with the therapeutic dosage ranges. Careful clinical monitoring is advised (see Dosage and Administration: Elderly and Pharmacokinetics: Elderly).
- Renal impairment: In patients with renal impairment, there is an increase in exposure of enoxaparin sodium which increases the risk of bleeding. Since exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30 ml/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 ml/min) and mild (creatinine clearance 50-80 ml/min) renal impairment, careful clinical monitoring is advised (see Dosage and Administration: Renal impairment and Pharmacokinetics: Renal impairment).
- Low weight: An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients (see Pharmacokinetics: Weight).

- **Obese Patients:** Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI >30 kg/m<sup>2</sup>) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.
- **Monitoring of platelet counts:** The risk of antibody-mediated heparin-induced thrombocytopenia also exists with Low Molecular Weight Heparins. Should thrombocytopenia occur, it usually appears between the 5<sup>th</sup> and the 21<sup>st</sup> day following the beginning of enoxaparin sodium treatment. Therefore, it is recommended that the platelet counts be measured before the initiation of therapy with enoxaparin sodium and then regularly thereafter during the treatment. In practice, if a confirmed significant decrease of the platelet count is observed (30 to 50 % of the initial value), enoxaparin sodium treatment must be immediately discontinued and the patient switched to another therapy.

#### **Driving a Vehicle or Performing Other Hazardous Tasks**

Enoxaparin sodium has no effect on the ability to drive and operate machines.

#### **Interactions**

It is recommended that agents which affect hemostasis should be discontinued prior to enoxaparin sodium therapy unless strictly indicated. These agents include medications such as:

- Systemic salicylates, acetylsalicylic acid, and NSAIDs including ketorolac,
- Dextran 40, ticlopidine and clopidogrel,
- Systemic glucocorticoids,
- Thrombolytics and anticoagulants,
- Other anti-platelet agents including glycoprotein IIb/IIIa antagonists.

If the combination is indicated, enoxaparin sodium should be used with careful clinical and laboratory monitoring when appropriate.

#### **Pregnancy**

Animal studies have not shown any evidence of fetotoxicity or teratogenicity. In the pregnant rat, the transfer of <sup>35</sup>S-enoxaparin sodium across the maternal placenta to the fetus is minimal.

In humans, there is no evidence that enoxaparin sodium crosses the placental barrier during the second trimester of pregnancy. There is no information available concerning the first and the third trimesters. As there are no adequate and well-controlled studies in pregnant women and because animal studies are not always predictive of human response, this drug should be used during pregnancy only if the physician has established a clear need. (See also Warnings: Pregnant women with mechanical prosthetic heart valves and Precautions: Mechanical prosthetic heart valves).

#### **Lactation**

In lactating rats, the concentration of 35S-enoxaparin sodium or its labelled metabolites in milk is very low. It is not known whether unchanged enoxaparin sodium is excreted in human breast milk. The oral absorption of enoxaparin sodium is unlikely. However, as a precaution, lactating mothers receiving enoxaparin sodium should be advised to avoid breast-feeding.

#### **Adverse Reactions**

Enoxaparin has been evaluated in more than 15,000 patients who received enoxaparin in clinical trials. These included 1776 for prophylaxis of deep vein thrombosis following orthopaedic or abdominal surgery in patients at risk for thromboembolic complications, 1169 for prophylaxis of deep vein thrombosis in acutely ill medical patients with severely restricted mobility, 559 for treatment of deep vein thrombosis with or without pulmonary embolism, 1578 for treatment of unstable angina and non-Q-wave myocardial infarction and 10,176 for treatment of acute ST-elevation myocardial infarction.

Enoxaparin sodium regimen administered during these clinical trials varies depending on indications. The enoxaparin sodium dose was 40 mg SC once daily for prophylaxis of deep vein thrombosis following surgery or in acutely ill medical patients with severely restricted mobility. In treatment of deep vein thrombosis (DVT) with or without pulmonary embolism (PE), patients receiving enoxaparin were treated with either a 1 mg/kg SC dose every 12 hours or a 1.5 mg/kg SC dose once a day. In the clinical studies for treatment of unstable angina and non-Q-wave myocardial infarction, doses were 1 mg/kg SC every 12 hours and in the clinical study for treatment of acute ST-segment elevation myocardial infarction enoxaparin sodium regimen was a 30 mg IV bolus followed by 1 mg/kg SC every 12 hours.

The adverse reactions observed in these clinical studies and reported in post-marketing experience are detailed below. Frequencies are defined as follows: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ) or not known (cannot be estimated from available data). Post-marketing adverse reactions are designated with a frequency “not known”.

### Haemorrhages

In clinical studies, haemorrhages were the most commonly reported reaction. These included major haemorrhages, reported at most in 4.2 % of the patients (surgical patients<sup>1</sup>). Some of these cases have been fatal.

As with other anticoagulants, haemorrhage may occur in the presence of associated risk factors such as: organic lesions liable to bleed, invasive procedures or the concomitant use of medications affecting haemostasis (see Section Precautions and Section Interactions).

<sup>1</sup> - In surgical patients, haemorrhage complications were considered major: (1) if the haemorrhage caused a significant clinical event or (2) if accompanied by an haemoglobin decrease  $\geq 2$  g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial haemorrhages were always considered major.

MedDRA system organ class	Prophylaxis in surgical patients	Prophylaxis in medical patients	Treatment in patients with DVT with or without PE	Treatment in patients with unstable angina and non-Q-wave MI	Treatment in patients with acute STEMI
<i>Vascular disorders</i>	<i>Very common:</i> <b>Haemorrhage *</b>  <i>Rare:</i> <b>Retroperitoneal haemorrhage</b>	<i>Common:</i> <b>Haemorrhage *</b>	<i>Very common:</i> <b>Haemorrhage *</b>  <i>Uncommon:</i> <b>Intracranial haemorrhage, Retroperitoneal haemorrhage</b>	<i>Common:</i> <b>Haemorrhage *</b>  <i>Rare:</i> <b>Retroperitoneal haemorrhage</b>	<i>Common:</i> <b>Haemorrhage *</b>  <i>Uncommon:</i> <b>Intracranial haemorrhage, Retroperitoneal haemorrhage</b>

\*: such as haematoma, ecchymosis other than at injection site, wound haematoma, haematuria, epistaxis and gastro-intestinal haemorrhage.

### Thrombocytopenia and thrombocytosis

MedDRA system organ class	Prophylaxis in surgical patients	Prophylaxis in medical patients	Treatment in patients with DVT with or without PE	Treatment in patients with unstable angina and non-Q-wave MI	Treatment in patients with acute STEMI
<i>Blood and lymphatic system disorders</i>	<i>Very common:</i> <b>Thrombocytosis*</b>  <i>Common:</i> <b>Thrombocytopenia</b>	<i>Uncommon:</i> <b>Thrombocytopenia</b>	<i>Very common:</i> <b>Thrombocytosis *</b>  <i>Common:</i> <b>Thrombocytopenia</b>	<i>Uncommon:</i> <b>Thrombocytopenia</b>	<i>Common:</i> <b>Thrombocytosis* Thrombocytopenia</b>  <i>Very rare:</i> <b>Immuno-allergic thrombocytopenia</b>

\*: Platelet increased  $> 400$  G/L

### **Other clinically relevant adverse reactions**

These reactions are presented below, whatever the indications, by system organ class, frequency grouping and decreasing order of seriousness.

MedDRA system organ class	All indications
Immune system disorders	<i>Common:</i> <b>Allergic reaction</b> <i>Rare:</i> <b>Anaphylactic / anaphylactoid reaction (see also Post marketing experience)</b>
Hepatobiliary disorders	<i>Very common:</i> <b>Hepatic enzymes increase (mainly transaminases **)</b>
Skin and subcutaneous tissue disorders	<i>Common:</i> <b>Urticaria, pruritus, erythema,</b> <i>Uncommon:</i> <b>Bullous dermatitis</b>
General disorders and administration site conditions	<i>Common:</i> <b>Injection site haematoma, injection site pain, other injection site reaction*</b> <i>Uncommon:</i> <b>Local irritation; skin necrosis at injection site</b>
Investigations	<i>Rare:</i> <b>Hyperkaliemia</b>

\*: such as injection site oedema, haemorrhage, hypersensitivity, inflammation, mass, pain, or reaction (NOS)

\*\*: transaminases levels > 3 times the upper limit of normality

#### Post marketing experience

The following adverse reactions have been identified during post approval use of Clexane®. The adverse reactions are derived from spontaneous reports and therefore, the frequency is “not known” (cannot be estimated from the available data)

- Immune System Disorders
  - Anaphylactic/anaphylactoid reaction including shock
- Nervous System Disorders
  - Headache
- Vascular Disorders
  - Cases of spinal haematoma (or neuraxial haematoma) have been reported with the concurrent use of enoxaparin sodium as well as spinal/epidural anaesthesia or spinal puncture. These reactions have resulted in varying degrees of neurologic injuries including long term or permanent paralysis.
- Blood and Lymphatic System Disorders:
  - Haemorrhagic anemia
  - Cases of immuno-allergic thrombocytopenia with thrombosis; in some of them thrombosis was complicated by organ infarction or limb ischaemia (see Precautions: Monitoring of platelet counts).
  - Eosinophilia
- Skin and subcutaneous disorders
  - Cutaneous vasculitis, skin necrosis usually occurring at the injection site (these phenomena have been usually preceded by purpura or erythematous plaques, infiltrated and painful). Treatment with enoxaparin sodium must be discontinued.
  - Injection site nodules (inflammatory nodules, which were not cystic enclosure of enoxaparin). They resolve after a few days and should not cause treatment discontinuation.
  - Alopecia
- Hepatobiliary disorders
  - Hepatocellular liver injury
  - Cholestatic liver injury

- Musculoskeletal and connective tissue disorders
  - Osteoporosis following long-term therapy (greater than 3 months)

## **Overdosage**

### **Signs and symptoms**

- **Symptoms and severity**

Accidental overdosage with enoxaparin sodium after intravenous, extracorporeal or subcutaneous administration may lead to hemorrhagic complications. Following oral administration of even large doses, it is unlikely that enoxaparin sodium will be absorbed.

## **Management**

- **Antidote and treatment**

The anticoagulant effects can be largely neutralized by the slow intravenous injection of protamine. The dose of protamine depends on the dose of enoxaparin sodium injected; 1 mg protamine neutralizes the anticoagulant effect of 1 mg of enoxaparin sodium, if enoxaparin sodium was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours previous to the protamine administration, or if it has been determined that a second dose of protamine is required. After 12 hours of the enoxaparin sodium injection, protamine administration may not be required. However, even with high doses of protamine, the anti-Xa activity of enoxaparin sodium is never completely neutralized (maximum about 60%).

## **Pharmacodynamics**

Enoxaparin sodium is a Low Molecular Weight Heparin with a mean molecular weight of approximately 4,500 daltons. The drug substance is the sodium salt. The molecular weight distribution is:

<2000 daltons ≤ 20%

2000 to 8000 daltons ≥ 68%

>8000 daltons ≤ 18%

Enoxaparin sodium is obtained by alkaline depolymerization of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enopyranosuronic acid group at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of the chain. About 20% (ranging between 15% and 25%) of the enoxaparin structure contains an 1,6 anhydro derivative on the reducing end of the polysaccharide chain. In the *in vitro* purified system, enoxaparin sodium has a high anti-Xa activity (approximately 100 IU/mg) and low anti-IIa or anti thrombin activity (approximately 28 IU/mg). These anticoagulant activities are mediated through anti-thrombin III (ATIII) resulting in anti-thrombotic activities in humans.

Beyond its anti-Xa/IIa activity, further anti-thrombotic and anti-inflammatory properties of enoxaparin have been identified in healthy subjects and patients as well as in non-clinical models.

These include ATIII-dependent inhibition of other coagulation factors like factor VIIa, induction of endogenous Tissue Factor Pathway Inhibitor (TFPI) release as well as a reduced release of von Willebrand factor (vWF) from the vascular endothelium into the blood circulation. These factors are known to contribute to the overall anti-thrombotic effect of enoxaparin.

- **Clinical efficacy/ Clinical Studies**

### **Treatment of unstable angina and non-Q-wave myocardial infarction**

In a large multicenter study, 3,171 patients enrolled at the acute phase of unstable angina or non-Q-wave myocardial infarction were randomized to receive in association with aspirin (100 to 325 mg once daily), either subcutaneous enoxaparin sodium 1mg/kg every 12 hours or intravenous unfractionated heparin adjusted based on activated partial thromboplastin time (aPTT). Patients had to be treated in hospital for a minimum of 2 days and a maximum of 8 days, until clinical stabilization, revascularization procedures or hospital discharge. The patients had to be followed up to 30 days. Enoxaparin sodium compared to heparin significantly decreased the incidence of recurrent angina, myocardial infarction and death, with a relative risk reduction of 16.2% at Day 14, sustained over the 30 day period. Furthermore, fewer patients in the enoxaparin sodium group underwent revascularization with either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) (15.8% relative risk reduction at Day 30).

### **Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI).**

In a large multicenter study, 20479 patients with STEMI eligible to receive fibrinolytic therapy were randomized to receive either enoxaparin sodium in a single 30-mg intravenous bolus plus a 1 mg/kg SC dose followed by an SC injection of 1.0 mg/kg every 12 hours or intravenous unfractionated heparin adjusted based on activated partial thromboplastin time (aPTT) for 48 hours. All patients were also treated with aspirin for a minimum of 30 days. The enoxaparin dosing strategy was adjusted for severe renally impaired patients and for the elderly of at least 75 years of

age. The SC injections of enoxaparin were given until hospital discharge or for a maximum of eight days (whichever came first).

4716 patients underwent percutaneous coronary intervention receiving antithrombotic support with blinded study drug. Therefore, for patients on enoxaparin, the PCI was to be performed on enoxaparin (no switch) using the regimen established in previous studies i.e. no additional dosing, if last SC administration given less than 8 hours before balloon inflation, IV bolus of 0.3 mg/kg enoxaparin, if the last SC administration given more than 8 hours before balloon inflation.

Enoxaparin sodium compared to unfractionated heparin significantly decreased the incidence of the primary end point, a composite of death from any cause or myocardial re-infarction in the first 30 days after randomization [9.9 percent in the enoxaparin group, as compared with 12.0 percent in the unfractionated heparin group] with a 17 percent relative risk reduction ( $P<0.001$ ).

The treatment benefits of enoxaparin, evident for a number of efficacy outcomes, emerged at 48 hours, at which time there was a 35 percent reduction in the relative risk of myocardial re-infarction, as compared with treatment with unfractionated heparin ( $P<0.001$ ).

The beneficial effect of enoxaparin on the primary end point was consistent across key subgroups including age, gender, infarct location, history of diabetes, history of prior myocardial infarction, type of fibrinolytic administered, and time to treatment with study drug.

There was a significant treatment benefit of enoxaparin, as compared with unfractionated heparin, in patients who underwent percutaneous coronary intervention within 30 days after randomization (23 percent reduction in relative risk) or who were treated medically (15 percent reduction in relative risk,  $P = 0.27$  for interaction). The rate of the 30 day composite endpoint of death, myocardial re-infarction or ICH (a measure of net clinical benefit) was significantly lower ( $p<0.0001$ ) in the enoxaparin group (10.1%) as compared to the heparin group (12.2%), representing a 17% relative risk reduction in favor of treatment with Clexane®.

The beneficial effect of enoxaparin on the primary end point observed during the first 30 days was maintained over a 12 month follow-up period.<sup>181</sup>

## **Pharmacokinetics**

- General characteristics**

The pharmacokinetic parameters of enoxaparin sodium have been studied primarily in terms of the time course of plasma anti-Xa activity and also by anti-IIa activity, at the recommended dosage ranges after single and repeated subcutaneous administration and after single intravenous administration. The quantitative determination of anti-Xa and anti-IIa pharmacokinetic activities was conducted by validated amidolytic methods with specific substrates and an enoxaparin standard calibrated against the international standard for LMWHs (NIBSC).

## **Absorption**

- Bioavailability and Absorption**

The absolute bioavailability of enoxaparin sodium after subcutaneous injection, based on anti-Xa activity, is close to 100%. Injection volume and dose concentration over the range 100-200 mg/ml does not affect pharmacokinetic parameters in healthy volunteers.

The mean maximum plasma anti-Xa activity is observed 3 to 5 hours after subcutaneous injection and achieves approximately 0.2, 0.4, 1.0 and 1.3 anti-Xa IU/ml following single-subcutaneous administration of 20 mg, 40 mg, 1 mg/kg and 1.5 mg/kg doses, respectively.

A 30 mg IV bolus immediately followed by a 1 mg/kg SC every 12 hours provided initial peak anti-Factor Xa levels of 1.16 IU/mL (n=16) and average exposure corresponding to 88% of steady-state levels. Steady-state is achieved on the second day of treatment.

Enoxaparin pharmacokinetics appear to be linear over the recommended dosage ranges. Intra-patient and inter-patient variability is low. After repeated subcutaneous administration of 40 mg once daily and 1.5 mg/kg once daily regimens in healthy volunteers, the steady-state is reached on day 2 with an average exposure ratio about 15% higher than after a single dose. Steady-state enoxaparin activity levels are well predicted by single dose pharmacokinetics. After repeated subcutaneous administration of the 1 mg/kg twice daily regimen, the steady-state is reached from day 3 to 4 with mean exposure about 65% higher than after a single dose and mean peak and trough levels of about 1.2 and 0.52 IU/ml,

respectively. Based on enoxaparin sodium pharmacokinetics, this difference in steady state is expected and within the therapeutic range.

Plasma anti-IIa activity after subcutaneous administration is approximately ten-fold lower than anti-Xa activity. The mean maximum anti-IIa activity is observed approximately 3 to 4 hours following subcutaneous injection and reaches 0.13 IU/ml and 0.19 IU/ml following repeated administration of 1 mg/kg twice daily and 1.5 mg/kg once daily, respectively.

- ***Distribution***

The volume of distribution of enoxaparin sodium anti-Xa activity is about 5 liters and is close to the blood volume.

- ***Metabolism***

Enoxaparin sodium is primarily metabolized in the liver by desulfation and/or depolymerization to lower molecular weight species with much reduced biological potency.

- ***Elimination***

Enoxaparin sodium is a low clearance drug with a mean anti-Xa plasma clearance of 0.74 L/h after a 1.5 mg/kg 6-hour intravenous infusion.

Elimination appears monophasic with a half-life of about 4 hours after a single subcutaneous dose to about 7 hours after repeated dosing.

Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments 40% of the dose.

- ***Special populations***

#### **Elderly**

Based on the results of a population pharmacokinetic analysis, the enoxaparin sodium kinetic profile is not different in elderly subjects compared to younger subjects when renal function is normal. However, since renal function is known to decline with age, elderly patients may show reduced elimination of enoxaparin sodium (see Precautions: Hemorrhage in the Elderly, Dosage and Administration: Elderly, and Pharmacokinetics: Renal impairment).

#### **Renal impairment**

A linear relationship between anti-Xa plasma clearance and creatinine clearance at steady-state has been observed, which indicates decreased clearance of enoxaparin sodium in patients with reduced renal function. Anti-Xa exposure represented by AUC, at steady-state, is marginally increased in mild (creatinine clearance 50-80 ml/min) and moderate (creatinine clearance 30-50 ml/min) renal impairment after repeated subcutaneous 40 mg once daily doses. In patients with severe renal impairment (creatinine clearance <30 ml/min), the AUC at steady state is significantly increased on average by 65% after repeated subcutaneous 40 mg once daily doses (see Precautions: Renal impairment and Dosage and Administration: Renal impairment).

#### **Weight**

After repeated subcutaneous 1.5 mg/kg once daily dosing, mean AUC of anti-Xa activity is marginally higher at steady state in obese healthy volunteers (BMI 30-48 kg/m<sup>2</sup>) compared to non-obese control subjects, while A<sub>max</sub> is not increased. There is a lower weight-adjusted clearance in obese subjects with subcutaneous dosing. When non-weight adjusted dosing was administered, it was found after a single subcutaneous 40 mg dose, that anti-Xa exposure is 52% higher in low-weight women (<45 kg) and 27% higher in low-weight men (<57 kg) when compared to normal weight control subjects (see Precautions: Low Weight).

#### **Hemodialysis**

In a single study, elimination rate appeared similar but AUC was two-fold higher than control population, after a single 0.25 or 0.50 mg/kg intravenous dose.

- ***Pharmacokinetic interactions***

No pharmacokinetic interactions were observed between enoxaparin and thrombolytics when administered concomitantly.

#### **Incompatibilities / Compatibilities**

Subcutaneous injection: Do not admix with other products.

**Intravenous (Bolus) Injection (for acute STEMI indication only):** Enoxaparin sodium may be safely administered with normal saline solution (0.9%) or 5% dextrose in water

**Storage**

Store at or below 25°C. Do not freeze prefilled syringes.

**Preparation and Handling**

See posology and method of administration. The prefilled disposable syringe is ready for immediate use.

**Manufactured by:**

Sanofi Winthrop Industrie, 180 Rue Jean Jaures, 94700 Maisons Alfort ,France

**Marketed by:**

Sanofi India Limited, Gala No. 3, 4, 5, 6B & 6C, 7F  
City Link Warehsg. Complex Building No. B3, S No.120-121 Vill. Vadpe – 421302  
Taluka : Bhiwandi-13 (Bhiwandi Corporation) , District : Thane Z5, Maharashtra

Revised December 2018

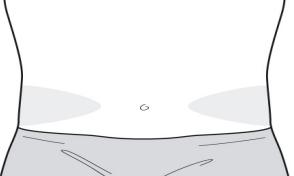
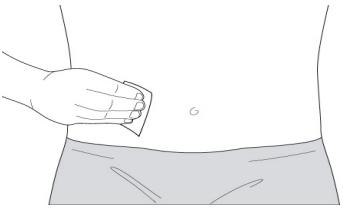
Ref: CCDS Ver 14 dated Oct 2018

**INSTRUCTIONS FOR USE: Subcutaneous injection technique**

In case of self-injection, the healthcare professional will show the patient how to administer the injections before the patient is released from hospital. It is essential to follow these instructions exactly. If the patient has questions, be sure to ask the healthcare professional to provide the explanations needed.

Proper subcutaneous (under the skin) injection is essential to prevent pain and bruising at the injection site.

To avoid accidental needle sticks after injection, the prefilled syringes are fitted with an automatic safety device.

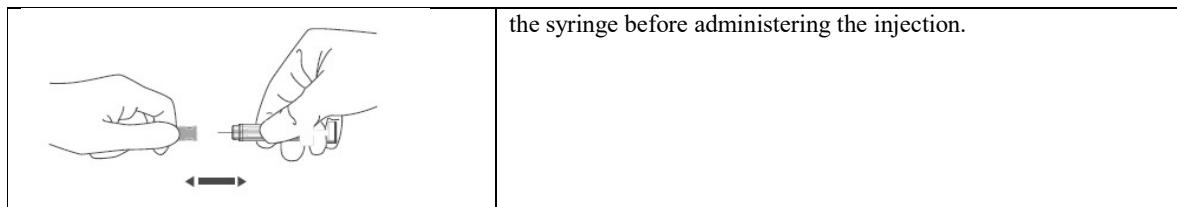
<b>Prepare the site for injection</b>	
	The recommended site for injection is into the fat of the lower abdomen. This should be at least 5 centimeters (2 inches) away from the belly button and out towards either side.
	Prior to injection, wash your hands. Cleanse (do not rub) the selected site for injection with an alcohol swab. Select a different site of lower abdomen for each injection.

**Prepare the syringe before the injection**

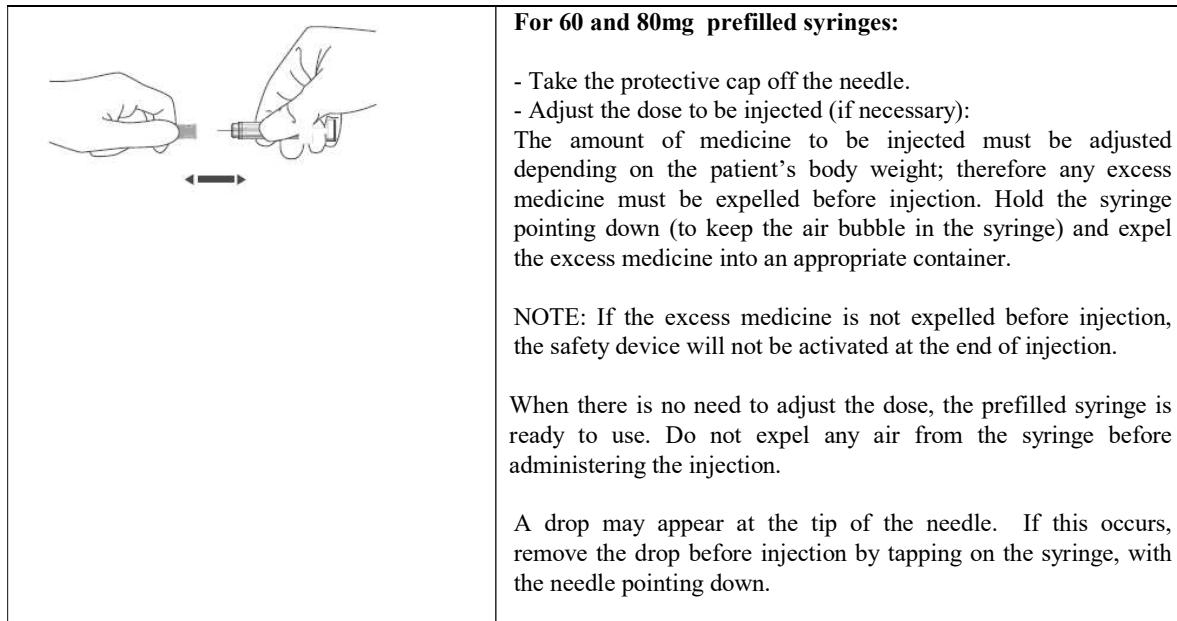
Check the expiry date on the label or carton. Do not use if the date has passed.

Check the syringe is not damaged and the medicine in it is a clear solution without particle. If the syringe is damaged or the medicine is not clear use another syringe.

	<b>For 20 and 40 mg doses:</b>  - Take the protective cap off the needle. A drop may appear at the tip of the needle. If this occurs, remove the drop before injection by tapping on the syringe, with the needle pointing down.  The prefilled syringe is ready to use. Do not expel any air from
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the syringe before administering the injection.



#### For 60 and 80mg prefilled syringes:

- Take the protective cap off the needle.

- Adjust the dose to be injected (if necessary):

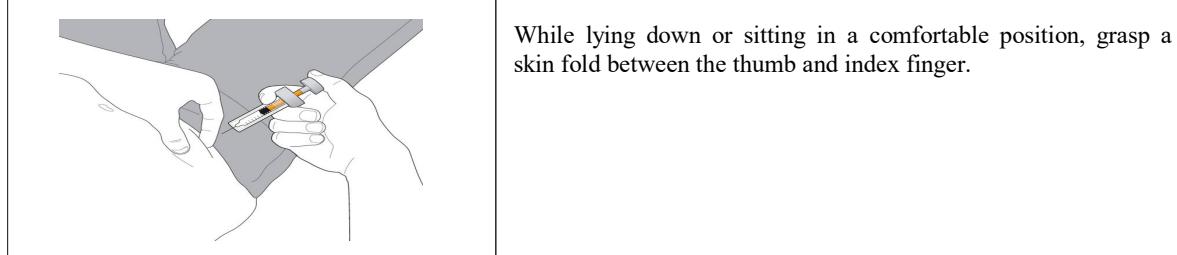
The amount of medicine to be injected must be adjusted depending on the patient's body weight; therefore any excess medicine must be expelled before injection. Hold the syringe pointing down (to keep the air bubble in the syringe) and expel the excess medicine into an appropriate container.

NOTE: If the excess medicine is not expelled before injection, the safety device will not be activated at the end of injection.

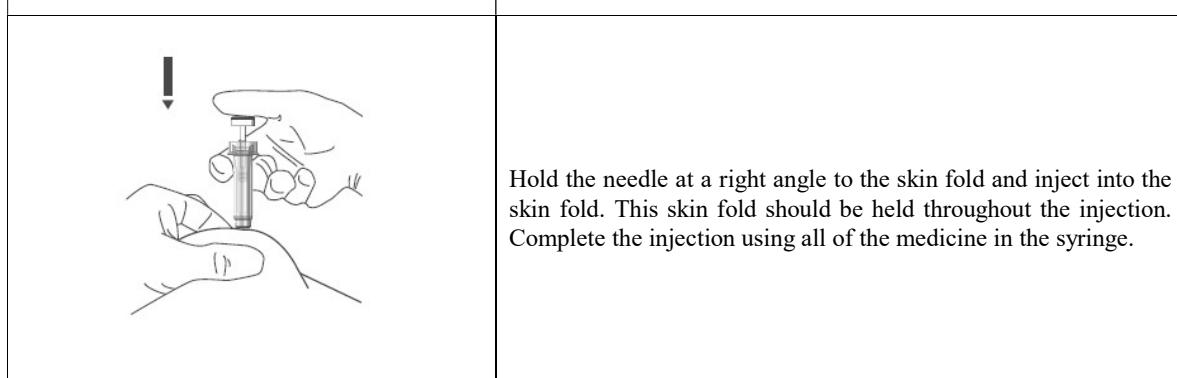
When there is no need to adjust the dose, the prefilled syringe is ready to use. Do not expel any air from the syringe before administering the injection.

A drop may appear at the tip of the needle. If this occurs, remove the drop before injection by tapping on the syringe, with the needle pointing down.

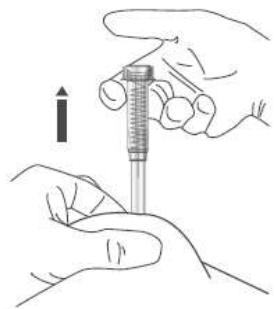
#### Administer the injection (all prefilled syringes: 20, 40, 60, 80 mg)



While lying down or sitting in a comfortable position, grasp a skin fold between the thumb and index finger.



Hold the needle at a right angle to the skin fold and inject into the skin fold. This skin fold should be held throughout the injection. Complete the injection using all of the medicine in the syringe.



Once the plunger is fully pressed down the safety device is activated automatically .This protects the used needle.  
Note: The plunger has to be pressed down all the way for the safety device to be activated.

Remove the syringe from the injection site.



Immediately dispose off the syringe in the nearest sharps container.

For more information contact your physician.



For use of only Registered Medical Practitioners  
or a Hospital or a Laboratory

## **Nilotinib 50mg, 150 mg and 200 mg capsules**

### **Tasigna®**

Antineoplastic agents - Protein-tyrosine kinase inhibitor

#### **Warning: QT PROLONGATION AND SUDDEN DEATHS**

Nilotinib prolongs the QT interval. Sudden deaths have been reported in patients receiving Nilotinib. It should not be used in patients with hypokalemia or hypomagnesimia, or long QT syndrome. Hypokalemia or hypomagnesimia must be corrected prior to Nilotinib administration and should be periodically monitored. Drugs known to prolong QT interval and strong CYP3A4 inhibitors should be avoided. Patients should avoid food 2 hours before and 1 hour after taking dose. Use with caution in patients with hepatic impairment. ECGs should be obtained to monitor the QTc at baseline, seven days after initiation and periodically thereafter, as well as following any dose adjustments.

### **Tasigna®**

Antineoplastic agents - Protein-tyrosine kinase inhibitor

#### **DESCRIPTION AND COMPOSITION**

##### **Pharmaceutical form**

Hard capsules.

##### **50 mg hard capsules**

White to yellowish powder in hard gelatin capsule with red opaque cap and light yellow opaque body, size 4 with black radial imprint “NVR/ABL” on cap.

##### **150 mg hard capsules**

White to yellowish powder in red opaque hard gelatin capsules, size 1 with black axial imprint “NVR/BCR”.

##### **200 mg hard capsules**

White to yellowish powder in light yellow opaque hard gelatin capsules, size 0 with red axial imprint “NVR/TKI”.

##### **Active substances**

##### **50 mg hard capsules:**

Each capsule contains 50 mg nilotinib base (as hydrochloride monohydrate)

##### **150 mg hard capsules**

Each capsule contains 150 mg nilotinib base (as hydrochloride, monohydrate).

## **200 mg hard capsules**

Each capsule contains 200 mg nilotinib base (as hydrochloride, monohydrate)

Certain dosage strengths and dosage forms may not be available in all countries.

### **Excipients**

#### **50 mg hard capsules**

**Capsule content:** Lactose monohydrate; Crospovidone; Poloxamer; Silica, colloidal anhydrous; Magnesium stearate.

**Capsule shell:** Gelatin; Titanium dioxide (E171); Iron oxide, red (E172); Iron oxide, yellow (E172).

**Printing ink:** Shellac; Iron oxide, black (E172); Propylene glycol; Ammonium hydroxide.

#### **150 mg hard capsules**

**Capsule content:** Lactose monohydrate; Crospovidone; Poloxamer; Silica colloidal, anhydrous/Colloidal silicon dioxide; Magnesium stearate

**Capsule shell:** Gelatin; Titanium dioxide (E 171); Iron oxide, red (E 172), Iron oxide, yellow (E 172)

**Printing ink:** Shellac; Iron oxide, black (E 172); n-Butyl alcohol; Propylene glycol; Dehydrated ethanol; Isopropyl alcohol; Ammonium hydroxide

#### **200 mg hard capsules**

**Capsule content:** Lactose monohydrate; Crospovidone; Poloxamer; Silica colloidal, anhydrous/Colloidal silicon dioxide; Magnesium stearate

**Capsule shell:** Gelatin; Titanium dioxide (E 171); Iron oxide, yellow (E 172)

**Printing ink:** Shellac; Dehydrated alcohol; Isopropyl alcohol; Butyl alcohol; Propylene glycol; Strong ammonia solution; Potassium hydroxide; Titanium dioxide; Industrial methylated spirit; Iron oxide, red (E 172), Iron oxide, black (E172)

Pharmaceutical formulations may vary between countries.

### **INDICATIONS**

Tasigna hard capsules are indicated for the:

- treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.  
*Patients who have been treated with Tasigna for at least 3 years and have achieved a sustained deep molecular response may be eligible for treatment discontinuation (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL STUDIES)*
- treatment of chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukemia (Ph+ CML) in adult patients resistant to or intolerant to at least one prior therapy including imatinib.  
*Ph+ CML patients in chronic phase, who have been previously treated with imatinib and whose treatment has been switched to Tasigna for at least 3 years and have achieved a sustained deep molecular response may be eligible for treatment discontinuation (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL STUDIES).*
- treatment of pediatric patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase.
- treatment of pediatric patients with chronic phase Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) with resistance or intolerance to prior therapy including imatinib.

## **DOSAGE REGIMEN AND ADMINISTRATION**

Tasigna is available in three dosage strengths (50 mg, 150 mg and 200 mg).

Treatment with Tasigna should be initiated by a physician experienced in the treatment of patients with CML.

Tasigna may be given in combination with hematopoietic growth factors such as erythropoietin or G-CSF if clinically indicated. Tasigna may be given with hydroxyurea or anagrelide if clinically indicated.

Monitoring of response to Tasigna therapy in Ph+ CML patients should be performed both routinely and when therapy is modified, to identify suboptimal response, loss of response to therapy, poor patient compliance, or possible drug-drug interaction. Results of monitoring should guide appropriate CML management.

### **General target population**

#### **Dosage in adult patients with newly diagnosed Ph+ CML- Chronic Phase (CP)**

The recommended dose of Tasigna is 300 mg twice daily (see section CLINICAL STUDIES). Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

#### **Dosage in newly diagnosed Ph+ CML-CP adult patients who have achieved a sustained deep molecular response (MR 4.5)**

Discontinuation of treatment may be considered in eligible Ph+ CML-CP patients who have been treated with Tasigna at 300 mg twice daily for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Discontinuation of Tasigna should be initiated by a physician experienced in the treatment of patients with CML (see sections WARNINGS AND PRECAUTIONS and CLINICAL STUDIES).

Patients who are eligible to discontinue Tasigna therapy must have their BCR-ABL transcript levels and complete blood count with differential monitored monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter. Monitoring of BCR-ABL transcript levels must be performed with a quantitative diagnostic test validated to measure molecular response levels on the International Scale (IS) with a sensitivity of at least MR4.5.

For patients who lose MR4.0 but not Major Molecular Response (MMR) during the treatment-free phase, BCR-ABL transcript levels should be monitored every 2 weeks until BCR-ABL levels return to a range between MR4.0 and MR4.5. Patients who maintain BCR-ABL levels between MMR and MR4.0 for a minimum of 4 consecutive measurements can return to the original monitoring schedule.

Patients who lose MMR must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Tasigna therapy should be re-initiated at 300 mg twice daily or at a reduced dose level of 400 mg once daily if the patient had a dose reduction prior to discontinuation of therapy. Patients who re-initiate Tasigna therapy should have their BCR-ABL transcript levels monitored monthly until MMR is re-established (see sections WARNINGS AND PRECAUTIONS AND CLINICAL STUDIES).

#### **Dosage in adult patients with Ph+ CML-CP and CML- Accelerated Phase (AP) resistant to or intolerant to at least one prior therapy including imatinib**

The recommended dose of Tasigna is 400 mg twice daily (see section CLINICAL STUDIES). Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

#### **Dosage in Ph+ CML-CP adult patients who have achieved a sustained deep molecular response (MR4.5) on Tasigna following prior imatinib therapy**

Discontinuation of treatment may be considered in eligible Ph+ CML-CP patients who have been treated with Tasigna for a minimum of 3 years if a deep molecular response is sustained for a minimum of one year immediately prior to discontinuation of therapy. Discontinuation of Tasigna should be initiated by a physician experienced in

the treatment of patients with CML (see sections WARNINGS AND PRECAUTIONS AND CLINICAL STUDIES).

Patients who are eligible to discontinue Tasigna therapy must have their BCR-ABL transcript levels and complete blood count with differential monitored monthly for one year, then every 6 weeks for the second year, and every 12 weeks thereafter. Monitoring of BCR-ABL transcript levels must be performed with a quantitative diagnostic test validated to measure molecular response levels on the International Scale (IS) with a sensitivity of at least MR4.5.

Patients with confirmed loss of MR4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR4.0) or loss of MMR must re-initiate treatment within 4 weeks of when loss of remission is known to have occurred. Tasigna therapy should be re-initiated at either 300 mg or 400 mg twice daily. Patients who re-initiate Tasigna therapy should have their BCR-ABL transcript levels monitored monthly until previous MMR or MR4.0 is re-established (see sections WARNINGS AND PRECAUTIONS And CLINICAL STUDIES).

#### **Dosage in pediatric patients with newly diagnosed Ph+ CML-CP or resistant or intolerant Ph+ CML-CP**

Dosing in pediatric patients is individualized and is based on body surface area ( $\text{mg}/\text{m}^2$ ). The recommended dose of Tasigna is  $230 \text{ mg}/\text{m}^2$  twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg) (see Table 1). Different strengths of Tasigna capsules can be combined to attain the desired dose. Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

There is no experience with treatment of pediatric patients below 2 years of age.

**Table 1 Pediatric dosing scheme of Tasigna  $230 \text{ mg}/\text{m}^2$  twice daily**

<b>Body Surface Area (BSA)</b>	<b>Dose in mg (twice daily)</b>
Up to $0.32 \text{ m}^2$	50 mg
$0.33 - 0.54 \text{ m}^2$	100 mg
$0.55 - 0.76 \text{ m}^2$	150 mg
$0.77 - 0.97 \text{ m}^2$	200 mg
$0.98 - 1.19 \text{ m}^2$	250 mg
$1.20 - 1.41 \text{ m}^2$	300 mg
$1.42 - 1.63 \text{ m}^2$	350 mg
$\geq 1.64 \text{ m}^2$	400 mg

#### **Monitoring recommendations and dose adjustments**

A baseline ECG is recommended prior to initiating therapy with Tasigna and should be repeated after 7 days and as clinically indicated. Hypokalemia or hypomagnesemia must be corrected prior to Tasigna administration and potassium and magnesium blood levels should be monitored periodically during therapy, particularly in patients at risk for these electrolyte abnormalities (see section WARNINGS AND PRECAUTIONS).

Increases in total serum cholesterol levels have been reported with Tasigna therapy (see section WARNINGS AND PRECAUTIONS). Lipid profiles should be determined prior to initiating Tasigna therapy, assessed at month 3 and 6 after initiating therapy, and at least yearly during chronic therapy.

Increases in blood glucose levels have been reported with Tasigna therapy (see section WARNINGS AND PRECAUTIONS). Blood glucose levels should be assessed prior to initiating Tasigna therapy and monitored during treatment.

Due to possible occurrence of Tumor Lysis Syndrome (TLS) correction of clinically significant dehydration and treatment of high uric acid levels are recommended prior to initiating therapy with Tasigna (see section ADVERSE DRUG REACTIONS).

Tasigna may need to be temporarily withheld and/or dose reduced for hematological toxicities (neutropenia, thrombocytopenia) that are not related to underlying leukemia (see Table 2).

**Table 2 Dose Adjustments for Neutropenia and Thrombocytopenia**

Adult patients with: - Newly diagnosed CML in chronic phase at 300 mg twice daily - Resistant or intolerant CML in chronic phase at 400 mg twice daily	ANC* $<1 \times 10^9/L$ and/or platelet counts $<50 \times 10^9/L$	1. Stop Tasigna, and monitor blood counts 2. Resume within 2 weeks at prior dose if ANC $>1 \times 10^9/L$ and/or platelets $>50 \times 10^9/L$ 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.
Adult patients with: resistant or intolerant CML in accelerated phase at 400 mg twice daily	ANC* $<0.5 \times 10^9/L$ and/or platelet counts $<10 \times 10^9/L$	1. Stop Tasigna, and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC $>1.0 \times 10^9/L$ and/or platelets $>20 \times 10^9/L$ . 3. If blood counts remain low, a dose reduction to 400 mg once daily may be required.
Pediatric patients with: - Newly diagnosed CML in chronic phase at $230 \text{ mg/m}^2$ twice daily - Resistant or intolerant CML in chronic phase at $230 \text{ mg/m}^2$ twice daily	ANC* $<1 \times 10^9/L$ and/or platelet counts $<50 \times 10^9/L$	1. Stop Tasigna and monitor blood counts. 2. Resume within 2 weeks at prior dose if ANC $>1.5 \times 10^9/L$ and/or platelets $>75 \times 10^9/L$ . 3. If blood counts remain low, a dose reduction to $230 \text{ mg/m}^2$ once daily may be required. 4. If event occurs after dose reduction, consider discontinuing treatment.

\*ANC = absolute neutrophil count

If clinically significant moderate or severe non-hematologic toxicity develops, dosing should be interrupted, and patients should be monitored and treated accordingly. If the prior dose was 300 mg twice daily in adult newly diagnosed patients with CML-CP or 400 mg twice daily in adult patients with resistant or intolerant CML-CP and CML-AP or  $230 \text{ mg/m}^2$  twice daily in pediatric patients, dosing may be resumed at 400 mg once daily in adult patients or at  $230 \text{ mg/m}^2$  once daily in pediatric patients once the toxicity has resolved. If the prior dose was 400 mg once daily in adult patients or  $230 \text{ mg/m}^2$  once daily in pediatric patients, treatment should be discontinued. If clinically appropriate, re-escalation of the dose in adult patients to 300 mg (newly diagnosed Ph+ CML-CP) or 400 mg (resistant or intolerant Ph+ CML-CP and CML-AP) twice daily or to  $230 \text{ mg/m}^2$  twice daily in pediatric patients should be attempted.

Elevated serum lipase: For Grade 3 to 4 lipase elevations, doses in adult patients should be reduced to 400 mg once daily or interrupted. In pediatric patients, treatment must be interrupted until the event returns to Grade  $\leq 1$ . Thereafter, if the prior dose was  $230 \text{ mg/m}^2$  twice daily, treatment can be resumed at  $230 \text{ mg/m}^2$  once daily. If the prior dose was  $230 \text{ mg/m}^2$  once daily, treatment should be discontinued. Serum lipase levels should be tested monthly or as clinically indicated (see sections WARNINGS AND PRECAUTIONS and ADVERSE DRUG REACTIONS).

Elevated bilirubin and hepatic transaminases: For Grade 3 to 4 bilirubin or hepatic transaminase elevations in adult patients, doses should be reduced to 400 mg once daily or interrupted. For Grade  $\geq 2$  bilirubin elevations or Grade  $\geq 3$  hepatic transaminase elevations in pediatric patients, treatment must be interrupted until the levels return to Grade  $\leq 1$ . Thereafter, if the prior dose was  $230 \text{ mg/m}^2$  twice daily, treatment can be resumed at  $230 \text{ mg/m}^2$  once daily. If the prior dose was  $230 \text{ mg/m}^2$  once daily, and recovery to Grade  $\leq 1$  takes longer than 28 days, treatment should be discontinued. Bilirubin and hepatic transaminases levels should be tested monthly or as clinically indicated (see section ADVERSE DRUG REACTIONS).

## **Special populations**

### **Renal impairment**

Clinical studies have not been performed in patients with impaired renal function. Clinical studies have excluded patients with serum creatinine concentration >1.5 times the upper limit of the normal range.

Since nilotinib and its metabolites are not renally excreted, a decrease in total body clearance is not anticipated in patients with renal impairment.

### **Hepatic impairment**

Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Dose adjustment is not considered necessary in hepatically impaired patients. Patients with hepatic impairment should be treated with caution (see section WARNINGS AND PRECAUTIONS).

### **Cardiac disorders**

In clinical studies, patients with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, or clinically significant bradycardia were excluded.

Caution should be exercised in patients with relevant cardiac disorders (see section WARNINGS AND PRECAUTIONS).

### **Pediatric patients (below 18 years)**

The safety and efficacy of Tasigna in pediatric patients with Ph+ CML-CP from 2 to less than 18 years of age have been established (see sections ADVERSE DRUG REACTIONS, CLINICAL PHARMACOLOGY, and CLINICAL STUDIES). There is no experience in pediatric patients below 2 years of age or in pediatric patients with Ph+ CML-AP or blast crisis (BC).

### **Geriatric patients (65 years or above)**

Approximately 12% and 30% of subjects in the clinical studies (newly diagnosed Ph+ CML-CP and resistant or intolerant Ph+ CML-CP and CML-AP) were 65 years of age or older. No major differences were observed for safety and efficacy in patients ≥65 years of age as compared to adults 18 to 65 years of age.

### **Method of administration**

Tasigna should be taken twice daily, at approximately 12 hour intervals, and must not be taken with food. The capsules should be swallowed whole with water. No food should be consumed for at least two hours before the dose is taken and no additional food should be consumed for at least one hour after the dose is taken (see sections WARNINGS AND PRECAUTIONS AND INTERACTIONS).

For patients who are unable to swallow capsules, the content of each capsule may be dispersed in one teaspoon of applesauce (pureed apple) and should be taken immediately. Not more than one teaspoon of applesauce and no food other than applesauce must be used (see section CLINICAL PHARMACOLOGY).

If a dose is missed the patient should not take an additional dose, but take the usual prescribed next dose.

## **CONTRAINDICATIONS**

Tasigna is contraindicated in patients with known hypersensitivity to nilotinib or to any of the excipients.

## **WARNINGS AND PRECAUTIONS**

### **Myelosuppression**

Treatment with Tasigna is often associated with thrombocytopenia, neutropenia and anemia (NCI CTC Grade 3/4). The occurrence is more frequent in patients with imatinib-resistant or intolerant CML and in particular in patients with CML-AP. Complete blood counts should be performed every two weeks for the first 2 months and then

monthly thereafter, or as clinically indicated. Myelosuppression was generally reversible and usually managed by withholding Tasigna temporarily or reducing the dose (see section DOSAGE REGIMEN AND ADMINISTRATION).

### QT Prolongation

*In vitro* data suggest that nilotinib has the potential to prolong cardiac ventricular repolarization (QT interval).

In the Phase III study in newly diagnosed Ph+ CML-CP patients the change from baseline in mean time-averaged QTcF interval at steady-state observed in the nilotinib 300 mg twice daily group was 6 msec. At the recommended dose of 300 mg twice daily no patient had an absolute QTcF of >480 msec and no events of Torsades de Pointes were observed.

In the Phase II study in imatinib-resistant or intolerant CML patients in chronic and accelerated phase, treated with nilotinib 400 mg twice daily, the change from baseline in mean time-averaged QTcF interval at steady-state was 5 msec and 8 msec, respectively. QTcF of >500 msec was observed in 4 patients (<1% of these patients).

In a healthy volunteer study with exposures that were comparable to the exposures observed in patients, the time-averaged mean placebo-subtracted QTcF change from baseline was 7 msec (CI ± 4 msec). No subject had a QTcF >450 msec. In addition, no clinically relevant arrhythmias were observed during the conduct of the trial. In particular, no episodes of Torsades de pointes (either transient or sustained) were observed.

Clinically meaningful prolongation of the QT interval may occur when Tasigna is inappropriately taken with food, and/or strong CYP3A4 inhibitors and/or medicinal products with a known potential to prolong QT interval; therefore, concomitant administration should be avoided (see section WARNINGS AND PRECAUTIONS: Food-Effects and section INTERACTIONS).

The presence of hypokalemia and hypomagnesemia may place patients at risk of developing QT prolongation (see section DOSAGE REGIMEN AND ADMINISTRATION).

Tasigna should be used with caution in patients who have or who are at significant risk of developing prolongation of QTc, such as those:

- with long QT syndrome,
- with uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina or clinically significant bradycardia.

### Sudden death

In clinical trials, uncommon cases (0.1 to 1%) of sudden death have been reported in patients in imatinib-resistant or -intolerant CML patients in chronic and accelerated phase receiving Tasigna with a past medical history of cardiac disease or significant cardiac risk factors. Comorbidities in addition to the underlying malignancy were also frequently present as were concomitant medications. Ventricular repolarization abnormalities may have been contributory factors. Based on post-marketing exposure in patient-years, the estimated reporting rate for spontaneous reports of sudden death is 0.02% per patient-year. No cases of sudden deaths have been reported in the newly diagnosed Ph+ CML-CP Phase III study.

### Cardiovascular events

Cardiovascular events were reported in a randomized, Phase III nilotinib trial in newly diagnosed CML patients and observed in the post-marketing reports. With a median time on therapy of 60.5 months in the clinical trial, Grade 3 / 4 cardiovascular events included peripheral arterial occlusive disease (1.4% and 1.1% at 300 mg and 400 mg twice a day respectively), ischemic heart disease (2.2% and 6.1% at 300 mg and 400 mg twice a day respectively) and ischemic cerebrovascular events (1.1% and 2.2% at 300 mg and 400 mg twice a day respectively). If acute signs or symptoms of cardiovascular events occur, advise patients to seek immediate medical attention. The cardiovascular status of patients should be evaluated and cardiovascular risk factors should be monitored and actively managed during Tasigna therapy according to standard guidelines (see section DOSAGE REGIMEN AND ADMINISTRATION).

## **Fluid retention**

Severe forms of drug-related fluid retention such as pleural effusion, pulmonary edema, and pericardial effusion were uncommonly (0.1 to 1%) observed in a Phase III study of newly diagnosed CML patients. Similar events were observed in post-marketing reports. Unexpected, rapid weight gain should be carefully investigated. If signs of severe fluid retention appear during treatment with nilotinib, the etiology should be evaluated and patients treated accordingly (see section DOSAGE REGIMEN AND ADMINISTRATION).

## **Hepatitis B reactivation**

Reactivation of hepatitis B can occur in patients who are chronic carriers of this virus after receiving a BCR-ABL tyrosine kinase inhibitor (TKI), such as nilotinib. Some cases involving drugs of the BCR-ABL TKI class resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome (see section ADVERSE DRUG REACTIONS).

Patients should be tested for hepatitis B infection before initiating treatment with nilotinib. Patients currently on nilotinib should have baseline testing for hepatitis B infection in order to identify chronic carriers of the virus. Experts in liver disease and in the treatment of hepatitis B should be consulted before treatment is initiated in patients with positive hepatitis B serology (including those with active disease) and for patients who test positive for hepatitis B infection during treatment. Carriers of hepatitis B virus who require treatment with nilotinib should be closely monitored for signs and symptoms of active hepatitis B infection throughout therapy and for several months following termination of therapy.

## **Special monitoring of Ph+ CML-CP adult patients who have achieved a sustained deep molecular response**

### **Eligibility for Discontinuation of Treatment**

Eligible patients who are confirmed to express the typical BCR-ABL transcripts, e13a2/b2a2 or e14a2/b3a2, can be considered for treatment discontinuation. Patients must have typical BCR-ABL transcripts to allow quantitation of BCR-ABL levels, evaluation of the depth of molecular response, and determination of a possible loss of molecular remission after Tasigna treatment discontinuation.

### **Monitoring of Patients who have discontinued therapy**

Monitoring of BCR-ABL transcript levels in patients eligible for treatment discontinuation must be performed with a quantitative diagnostic test validated to measure molecular response levels with a sensitivity of at least MR4.5. BCR-ABL transcript levels must be assessed prior to and during treatment discontinuation (see sections DOSAGE REGIMEN AND ADMINISTRATION and CLINICAL STUDIES).

Loss of MMR or confirmed loss of MR4.0 (two consecutive measures separated by at least 4 weeks showing loss of MR4.0) will trigger treatment re-initiation within 4 weeks of when loss of remission is known to have occurred. Frequent monitoring of BCR-ABL transcript levels and complete blood count with differential is required to detect possible loss of remission (see sections DOSAGE REGIMEN AND ADMINISTRATION AND CLINICAL STUDIES). For patients who fail to achieve MMR after three months of treatment re-initiation, BCR-ABL kinase domain mutation testing should be performed.

## **Special Populations**

### **Pediatric patients (below 18 years)**

The long-term effects of prolonged treatment with Tasigna in children and adolescents are unknown.

## **Laboratory tests and monitoring**

### **Blood lipids**

In a Phase III study in newly diagnosed CML patients, 1.1% of the patients treated with 400 mg nilotinib twice a day had a Grade 3/4 elevation in total cholesterol; however, there were no Grade 3/4 elevations in the 300 mg twice a day dose group (see section ADVERSE DRUG REACTIONS). It is recommended that the lipid profiles be determined before initiating treatment with Tasigna, assessed at month 3 and 6 after initiating therapy, and at least yearly during chronic therapy (see section DOSAGE REGIMEN AND ADMINISTRATION). If a HMG

CoA reductase inhibitor (a lipid lowering agent) is needed, please refer to section INTERACTIONS, before starting treatment since certain HMG CoA reductase inhibitors are metabolized by the CYP3A4 pathway.

### **Blood glucose**

In a Phase III study in newly diagnosed CML patients, 6.9% of the patients treated with 400 mg nilotinib twice a day had a Grade 3/4 elevation in blood glucose; and 7.2% of the patients treated with 300 mg nilotinib twice a day had a Grade 3/4 elevation in blood glucose. It is recommended that the glucose levels should be assessed before initiating treatment with Tasigna and monitored during treatment as clinically indicated (see section DOSAGE REGIMEN AND ADMINISTRATION). If test results warrant therapy, physicians should follow their local standards of practice and treatment guidelines.

### **Interactions**

The administration of Tasigna with agents that are strong CYP3A4 inhibitors and drugs that may prolong the QT interval such as anti-arrhythmic medicines should be avoided (see section DOSAGE REGIMEN AND ADMINISTRATION and INTERACTIONS). Should treatment with any of these agents be required, it is recommended that therapy with Tasigna be interrupted if possible (see section INTERACTIONS). If transient interruption of treatment with Tasigna is not possible, close monitoring of the individual for prolongation of the QT interval is indicated (see sections DOSAGE REGIMEN AND ADMINISTRATION, INTERACTIONS AND CLINICAL PHARMACOLOGY).

Concomitant use of Tasigna with medicinal products that are potent inducers of CYP3A4 is likely to reduce exposure to nilotinib to a clinically relevant extent. Therefore, in patients receiving Tasigna, concomitant use of alternative therapeutic agents with less potential for CYP3A4 induction should be selected (see section INTERACTIONS).

### **Food Effects**

The bioavailability of nilotinib is increased by food. Tasigna must not be taken in conjunction with food (see sections DOSAGE REGIMEN AND ADMINISTRATION AND INTERACTIONS) and should be taken 2 hours after a meal. No food should be consumed for at least one hour after the dose is taken.

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time.

### **Hepatic Impairment**

Hepatic impairment has a modest effect on the pharmacokinetics of nilotinib. Single dose administration of nilotinib resulted in increases in AUC of 35%, 35% and 19% in subjects with mild, moderate and severe hepatic impairment respectively, compared to a control group of subjects with normal hepatic function. The predicted steady-state Cmax of nilotinib showed an increase of 29%, 18% and 22% respectively. Clinical studies have excluded patients with ALT and/ or AST >2.5 (or >5, if related to disease) times the upper limit of the normal range and/ or total bilirubin >1.5 times the upper limit of the normal range. Metabolism of nilotinib is mainly hepatic. Caution is recommended in patients with hepatic impairment (see monitoring recommendations in section DOSAGE REGIMEN AND ADMINISTRATION).

### **Serum Lipase**

Elevation in serum lipase has been observed. Caution is recommended in patients with previous history of pancreatitis. In case lipase elevations are accompanied by abdominal symptoms, doses should be interrupted and appropriate diagnostics should be considered in order to exclude pancreatitis (see section DOSAGE REGIMEN AND ADMINISTRATION).

### **Total gastrectomy**

The bioavailability of nilotinib might be reduced in patients with total gastrectomy (see section CLINICAL PHARMACOLOGY). More frequent follow-up of these patients should be considered.

## **Tumor lysis syndrome**

Cases of tumor lysis syndrome have been reported in patients treated with Tasigna. For monitoring recommendations please refer to section DOSAGE REGIMEN AND ADMINISTRATION.

## **ADVERSE DRUG REACTIONS**

### **Summary of the safety profile**

The nilotinib safety profile described below is based on data from adult patients with newly diagnosed Ph+ CML-CP in a randomized, open label, active comparator-controlled phase-III trial and adult patients with resistant or intolerant Ph+ CML-CP and CML-AP which served as a basis for the listed indications (see Table 3 and section INDICATIONS). Safety information from two Tasigna treatment discontinuation studies in adult patients and from a Phase III study in adult patients with Ph+ CML in chronic phase with suboptimal response to imatinib is also provided.

#### **In adult patients with newly diagnosed Ph+ CML-CP**

The data reported below reflect exposure to Tasigna from a randomized phase III study in adult patients with newly diagnosed Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279). The median time on treatment was 60.5 months (range 0.1 to 70.8 months).

Non-hematologic adverse drug reactions (ADRs) reported with very common frequency ( $\geq 10\%$ ) were rash, pruritus, headache, nausea, fatigue, alopecia, myalgia, and upper abdominal pain. Most of these ADRs were mild to moderate in severity (Grade 1 or 2). Constipation, diarrhoea, dry skin, muscle spasms, arthralgia, abdominal pain, peripheral oedema, vomiting and asthenia were observed less commonly (<10% and  $\geq 5\%$ ) and have been of mild to moderate severity, manageable and generally did not require dose reduction. Pleural and pericardial effusions, regardless of causality, occurred in 2% and <1% of patients, respectively, receiving Tasigna 300 mg twice daily. Gastrointestinal haemorrhage, regardless of causality, was reported in 3% of these patients.

The change from baseline in mean time-averaged QTcF interval at steady-state in the nilotinib recommended dose of 300 mg twice daily was 6 msec. In the nilotinib 400 mg twice daily group and the imatinib 400 mg once daily group the change from baseline in mean time-averaged QTcF interval at steady-state was 6 msec and 3 msec, respectively. No patient had an absolute QTcF of >500 msec while on study drug in any of the Tasigna treatment groups and no events of Torsades de Pointes were observed. QTcF increase from baseline that exceeds 60 msec was observed in 5 patients while on Tasigna (one in the 300 mg twice daily treatment group and four in the 400 mg twice daily treatment group).

No patients in any treatment group had a LVEF <45% during treatment. Also, there were no patients with 15% or greater decrease from baseline in LVEF.

No sudden deaths have been reported in any treatment group.

In the nilotinib 300 mg twice daily group, haematologic ADRs include myelosuppression: thrombocytopenia (18%), neutropenia (15%), and anaemia (8%). Biochemistry ADRs include alanine aminotransferase increased (24%), hyperbilirubinaemia (16%), aspartate aminotransferase increased (12%), lipase increased (11%), blood bilirubin increased (10%), hyperglycaemia (4%), hypercholesterolaemia (3%), and hypertriglyceridaemia (<1%). See Table 5 for Grade 3/4 laboratory abnormalities.

Discontinuation due to adverse drug reactions was observed in 10% of patients.

#### **In adult patients with resistant or intolerant Ph+ CML-CP and CML-AP**

The data reported below reflect exposure to Tasigna in 458 adult patients with Ph+ CML-CP (n=321) and CML-AP (n=137) resistant to or intolerant to at least one prior therapy including imatinib in an open-label multicenter study treated at the recommended dose of 400 mg twice daily.

Non-haematologic ADRs reported with very common frequency ( $\geq 10\%$  in the combined CML-CP and CML-AP patient populations) were rash, pruritus, nausea, fatigue, headache, constipation, diarrhoea, vomiting and myalgia. Most of these ADRs were mild to moderate in severity. Alopecia, muscle spasms, decreased appetite, arthralgia,

bone pain, abdominal pain, peripheral oedema and asthenia were observed less frequently (<10% and >5%) and have been of mild to moderate severity (Grade 1 or 2).

Pleural and pericardial effusions as well as complications of fluid retention occurred in <1% of patients receiving Tasigna. Cardiac failure was observed in <1% of patients. Gastrointestinal and central nervous system (CNS) haemorrhage was reported in 1% and <1% of patients, respectively.

QTcF exceeding 500 msec was observed in this study in 4 patients (<1%). No episodes of Torsades de Pointes (transient or sustained) were observed.

Haematologic ADRs include myelosuppression: thrombocytopenia (31%), neutropenia (17%), and anaemia (14%). See Table 5 for Grade 3/4 laboratory abnormalities.

Discontinuation due to adverse drug reactions was observed in 16% of CP and 10% of AP patients.

#### **In adult patients with Ph+ CML-CP who have not achieved a molecular response greater than or equal to a 4.5-log reduction with imatinib treatment**

The data reported below were generated in a randomized, open-label, Phase III study where adult male and female patients diagnosed with Ph+ CML-CP and after two years of imatinib therapy were exposed to Tasigna 400 mg twice daily versus imatinib 400 mg or 600 mg once daily for 48 months. Patients randomized to the imatinib arm received the same dose of imatinib as prior to randomization. The median duration of exposure was 47.2 months in the Tasigna arm and 37.0 months and 26.7 months in the 400 mg and 600 mg dose cohorts of the imatinib arm, respectively.

The adverse drug reactions reported by at least 20% of the patients in the Tasigna group and more frequently compared to the imatinib group were headache, rash, and pruritus. A greater proportion of patients in the Tasigna group reported adverse events (AEs) leading to discontinuation and AEs requiring dose adjustment/interruption compared to those in the imatinib group. Increases in bilirubin and transaminases were commonly reported following Tasigna treatment.

Up to the 48-month cut-off date, three on-treatment deaths have been observed (two in the Tasigna arm and one in the imatinib arm). Three patients died more than 28 days after study drug discontinuation (one in the Tasigna arm and two in the imatinib arm).

QTc intervals >450 ms were observed in 4 patients receiving Tasigna therapy on Day 8. No patient had a QTc interval >480 ms. Increases in QTc interval from baseline of >30 ms were reported for 8 patients (7.9%). No patient experienced QTc prolongation >60 ms in the Tasigna group.

#### **Most Frequently Reported Adverse Drug Reactions**

Non-haematologic ADRs (excluding laboratory abnormalities) that were reported in at least 5% of the adult patients in any of the Tasigna clinical studies that serve as a basis for the listed indications are shown in Table 3. These are ranked under heading of frequency, the most frequent first. Within each frequency grouping adverse drug reactions are presented in order of decreasing seriousness. In addition the corresponding frequency category for each adverse drug reaction is based on the following (CIOMS III) convention: very common ( $\geq 1/10$ ) or common ( $\geq 1/100$  to  $<1/10$ ). The frequency is based on the highest for any Tasigna group in the two studies, using one decimal precision for percentages.

**Table 3** Most Frequently Reported Non-haematologic Adverse Drug Reactions ( $\geq 5\%$  in any Tasigna Group)

			Newly Diagnosed Ph+ CML-CP						Resistant or Intolerant Ph+ CML-CP and CML-AP						
			60-month analysis						24-month analysis						
			Tasigna 300 mg twice daily	Tasigna 400 mg twice daily	Imatinib 400 mg once daily	Tasigna 300 mg twice daily	Tasigna 400 mg twice daily	Imatinib 400 mg once daily	Tasigna 400 mg twice daily						
System Organ Class	Frequency	Adverse Drug Reaction	ALL GRADES (%)			GRADE 3 or 4 (%)			ALL GRADES (%)	GRADE 3/4 (%)	CML-CP GRADE 3/4 (%)	CML-AP GRADE 3/4 (%)			
			N=279 %	N=277 %	N=280 %	N=279 %	N=277 %	N=280 %	N=458 %	N=458 %	N=321 %	N=137 %			
			Metabolism and nutrition disorders	Common	Decreased appetite <sup>1</sup>	4	4	3	0	0	0	8	<1	<1	0
			Nervous system disorders	Very common	Headache	16	22	10	2	1	<1	15	1	2	<1
			Gastrointestinal disorders	Very common	Nausea	14	21	35	<1	1	<1	20	<1	<1	<1
				Very common	Constipation	10	7	3	0	<1	0	12	<1	<1	0
				Very common	Diarrhoea	9	7	31	<1	0	3	11	2	2	<1
				Very common	Vomiting	6	9	19	0	1	0	10	<1	<1	0
				Very common	Abdominal pain upper	10	9	8	1	0	<1	5	<1	<1	0
				Common	Abdominal pain	6	6	4	0	<1	0	6	<1	<1	<1

			Newly Diagnosed Ph+ CML-CP						Resistant or Intolerant Ph+ CML-CP and CML-AP					
			60-month analysis						24-month analysis					
			Tasigna 300 mg twice daily	Tasigna 400 mg twice daily	Imatinib 400 mg once daily	Tasigna 300 mg twice daily	Tasigna 400 mg twice daily	Imatinib 400 mg once daily	Tasigna 400 mg twice daily	ALL GRADES (%)	GRADE 3 or 4 (%)	ALL GRADES (%)	GRADE 3/4 (%)	CML-CP GRADE 3/4 (%)
System Organ Class	Frequency	Adverse Drug Reaction	N=279 %	N=277 %	N=280 %	N=279 %	N=277 %	N=280 %	N=458 %	N=458 %	N=321 %	N=137 %		
	Common	Dyspepsia	5	5	6	0	<1	0	3	0	0	0		
<b>Skin and subcutaneous tissue disorders</b>	Very common	Rash	33	39	14	<1	3	2	28	1	2	0		
	Very common	Pruritus	18	16	5	<1	<1	0	24	<1	<1	0		
	Very common	Alopecia	10	14	6	0	0	0	9	0	0	0		
	Very Common	Dry Skin	10	12	5	0	0	0	5	0	0	0		
	Common	Erythema	3	6	3	0	0	0	5	<1	<1	0		

			Newly Diagnosed Ph+ CML-CP						Resistant or Intolerant Ph+ CML-CP and CML-AP			
			60-month analysis						24-month analysis			
			Tasigna 300 mg twice daily	Tasigna 400 mg twice daily	Imatinib 400 mg once daily	Tasigna 300 mg twice daily	Tasigna 400 mg twice daily	Imatinib 400 mg once daily	Tasigna 400 mg twice daily			
			ALL GRADES (%)			GRADE 3 or 4 (%)			ALL GRADES (%)	GRADE 3/4 (%)	CML-CP GRADE 3/4 (%)	CML-AP GRADE 3/4 (%)
System Organ Class	Frequency	Adverse Drug Reaction	N=279 %	N=277 %	N=280 %	N=279 %	N=277 %	N=280 %	N=458 %	N=458 %	N=321 %	N=137 %
<b>Musculoskeletal and connective tissue disorders</b>	Very common	Myalgia	10	12	13	<1	<1	<1	10	<1	<1	<1
	Very Common	Arthralgia	8	10	8	<1	0	<1	7	<1	1	0
	Common	Muscle spasms	9	9	30	0	<1	1	8	<1	<1	0
	Common	Bone pain	4	5	4	0	<1	<1	6	<1	<1	0
	Common	Pain in extremity	5	3	8	<1	<1	<1	5	<1	<1	<1
<b>General disorders and administration site conditions</b>	Very common	Fatigue	12	11	13	0	<1	1	17	1	1	<1
	Common	Asthenia	9	5	9	<1	<1	0	6	0	0	0
	Common	Oedema peripheral	5	7	18	<1	0	0	6	0	0	0

<sup>1</sup> Also includes preferred term anorexia

Percentages are rounded to integer for presentation in this table. However, percentages with one decimal precision are used to identify terms with a frequency of at least 5% and to classify terms according to frequency categories

## **Additional Data from Clinical Trials**

The following adverse drug reactions were reported in adult patients in the Tasigna clinical studies which serve as a basis for the listed indications at the recommended doses at a frequency of less than 5% (common is  $\geq 1/100$  to  $<1/10$ ; uncommon is  $\geq 1/1,000$  to  $<1/100$ ; single events are captured as frequency not known) (Table 4). For laboratory abnormalities, very common events ( $\geq 1/10$ ) not included in Table 3 are also reported. These adverse drug reactions are included based on clinical relevance and ranked in decreasing order of seriousness within each category, obtained from two clinical studies: 1. Newly diagnosed Ph+ CML-CP 60 months' analysis and 2. Resistant or intolerant Ph+ CML-CP and CML-AP 24 months' analysis.

**Table 4 Adverse drug reactions reported in clinical studies in adult patients**

<b>Infections and infestations</b>	
Common:	Folliculitis, upper respiratory tract infection (including pharyngitis, nasopharyngitis, rhinitis)
Uncommon:	Pneumonia, bronchitis, urinary tract infection, herpes virus infection, candidiasis (including oral candidiasis), gastroenteritis
Not known:	Sepsis, subcutaneous abscess, anal abscess, furuncle, tinea pedis, hepatitis B reactivation
<b>Neoplasms Benign, Malignant and Unspecified</b>	
Common:	Skin papilloma
Not known:	Oral papilloma, paraproteinaemia
<b>Blood and lymphatic system disorders</b>	
Common:	Leukopenia, eosinophilia, febrile neutropenia, pancytopenia, lymphopenia
Not known:	Thrombocythaemia, leukocytosis
<b>Immune system disorders</b>	
Not known:	Hypersensitivity
<b>Endocrine disorders</b>	
Uncommon:	Hyperthyroidism, hypothyroidism
Not known:	Hyperparathyroidism secondary, thyroiditis
<b>Metabolism and nutrition disorders</b>	
Very common:	Hypophosphataemia (including blood phosphorus decreased)
Common:	Electrolyte imbalance (including hypomagnesaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypocalcaemia, hypercalcemia, hyperphosphataemia), diabetes mellitus, hyperglycaemia, hypercholesterolaemia, hyperlipidaemia, hypertriglyceridaemia
Uncommon:	Gout, dehydration, increased appetite, dyslipidaemia
Not known:	Hyperuricaemia, hypoglycaemia
<b>Psychiatric disorders</b>	
Common:	Depression, insomnia, anxiety
Not known:	Disorientation, confusional state, amnesia, dysphoria
<b>Nervous system disorders</b>	
Common:	Dizziness, peripheral neuropathy, hypoesthesia, paraesthesia
Uncommon:	Intracranial haemorrhage, ischaemic stroke, transient ischaemic attack, cerebral infarction, migraine, loss of consciousness (including syncope), tremor, disturbance in attention, hyperaesthesia
Not known:	Cerebrovascular accident, basilar artery stenosis, brain oedema, optic neuritis, lethargy, dysaesthesia, restless legs syndrome
<b>Eye disorders</b>	
Common:	Eye haemorrhage, periorbital oedema, eye pruritus, conjunctivitis, dry eye (including xerophthalmia)

Uncommon:	Vision impairment, vision blurred, visual acuity reduced, eyelid oedema, photopsia, hyperaemia (scleral, conjunctival, ocular), eye irritation, conjunctival haemorrhage
Not known:	Papilloedema, diplopia, photophobia, eye swelling, blepharitis, eye pain, chorioretinopathy, conjunctivitis allergic, ocular surface disease

#### **Ear and labyrinth disorders**

Common:	Vertigo
Not known:	Hearing impaired, ear pain, tinnitus

#### **Cardiac disorders**

Common:	Angina pectoris, arrhythmia (including atrioventricular block, cardiac flutter, extrasystoles, atrial fibrillation, tachycardia, bradycardia), palpitations, electrocardiogram QT prolonged
Uncommon:	Cardiac failure, myocardial infarction, coronary artery disease, cardiac murmur, pericardial effusion, cyanosis
Not known:	Ventricular dysfunction, pericarditis, ejection fraction decrease

#### **Vascular disorders**

Common:	Hypertension, flushing
Uncommon:	Hypertensive crisis, peripheral arterial occlusive disease, intermittent claudication, arterial stenosis limb, haematoma, arteriosclerosis
Not known:	Shock haemorrhagic, hypotension, thrombosis, peripheral artery stenosis

#### **Respiratory, thoracic and mediastinal disorders**

Common:	Dyspnoea, dyspnoea exertional, epistaxis, cough, dysphonia
Uncommon:	Pulmonary oedema, pleural effusion, interstitial lung disease, pleuritic pain, pleurisy, pharyngolaryngeal pain, throat irritation
Not known:	Pulmonary hypertension, wheezing, oropharyngeal pain

#### **Gastrointestinal disorders**

Common:	Pancreatitis, abdominal discomfort, abdominal distension, dyspepsia, dysgeusia, flatulence
Uncommon:	Gastrointestinal haemorrhage, melena, mouth ulceration, gastroesophageal reflux, stomatitis, oesophageal pain, dry mouth, gastritis, sensitivity of teeth
Not known:	Gastrointestinal ulcer perforation, retroperitoneal haemorrhage, haematemesis, gastric ulcer, oesophagitis ulcerative, subileus, enterocolitis, haemorrhoids, hiatus hernia, rectal haemorrhage, gingivitis

#### **Hepatobiliary disorders**

Very Common:	Hyperbilirubinaemia (including blood bilirubin increased)
Common:	Hepatic function abnormal
Uncommon:	Hepatotoxicity, toxic hepatitis, jaundice
Not known:	Cholestasis, hepatomegaly

#### **Skin and subcutaneous tissue disorders**

Common:	Night sweats, eczema, urticaria, hyperhidrosis, contusion, acne, dermatitis (including allergic, exfoliative and acneiform)
Uncommon:	Exfoliative rash, drug eruption, pain of skin, ecchymosis, swelling face
Not known:	Psoriasis, erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysaesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discolouration, skin exfoliation, skin hyperpigmentation, skin hypertrophy, hyperkeratosis

#### **Musculoskeletal and connective tissue disorders**

Common:	Musculoskeletal chest pain, musculoskeletal pain, back pain, neck pain, flank pain, muscular weakness
Uncommon:	Musculoskeletal stiffness, joint swelling
Not known:	Arthritis

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**Renal and urinary disorders**

Common:	Pollakiuria
Uncommon:	Dysuria, micturition urgency, nocturia
Not known:	Renal failure, hematuria, urinary incontinence, chromaturia

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**Reproductive system and breast disorders**

Uncommon:	Breast pain, gynaecomastia, erectile dysfunction
Not known:	Breast induration, menorrhagia, nipple swelling

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**General disorders and administration site conditions**

Common:	Pyrexia, chest pain (including non-cardiac chest pain), pain, chest discomfort, malaise
Uncommon:	Face oedema, gravitational oedema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold)
Not known:	Localized oedema

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**Investigations**

Very common:	Alanine aminotransferase increased, aspartate amino-transferase increased, lipase increased, lipoprotein cholesterol (including low density and high density) increased, total cholesterol increased, blood triglycerides increased
Common:	Haemoglobin decreased, blood amylase increased, gamma-glutamyltransferase increased, blood creatine phosphokinase increased, blood alkaline phosphatase increased, blood insulin increased, weight decreased, weight increased, globulins decreased
Uncommon:	Blood lactate dehydrogenase increased, blood urea increased
Not known:	Troponin increased, blood bilirubin unconjugated increased, blood insulin decreased, insulin C-peptide decreased, blood parathyroid hormone increased

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**Laboratory abnormalities**

Clinically relevant or severe abnormalities of routine haematologic or biochemistry laboratory values in adult patients are presented in Table 5.

**Table 5 Grade 3/4 Laboratory abnormalities**

	Newly diagnosed Ph+ CML-CP			Resistant or intolerant Ph+	
	Tasigna 300 mg twice daily N = 279	Tasigna 400 mg twice daily N = 277	Imatinib 400 mg once daily N = 280	Tasigna 400 mg twice daily CML-CP N=321	Tasigna 400 mg twice daily CML-AP N=137
<b>Haematologic Parameters</b>					
Myelosuppression					
-Neutropenia	12%	11%	22%	31%	42%
-Thrombocytopenia	10%	12%	9%	30%	42%
-Anaemia	4%	5%	6%	11%	27%
<b>Biochemistry Parameters</b>					
-Elevated creatinine	0%	0%	<1%	1%	<1%
-Elevated lipase	9%	10%	4%	18%	18%
-Elevated SGOT (AST)	1%	3%	1%	3%	2%
-Elevated SGPT (ALT)	4%	9%	3%	4%	4%
-Hypophosphataemia	8%	10%	10%	17%	15%

-Elevated Bilirubin (total)	4%	9%	<1%	7%	9%
-Elevated glucose	7%	7%	<1%	12%	6%
-Elevated Cholesterol (total)	0%	1%	0%	*	*
-Elevated tri-glycerides	0%	<1%	0	*	*

Percentages with one decimal precision are used and rounded to integer for presentation in this table.

\* parameter not collected

### Treatment discontinuation in adult Ph+ CML-CP patients who have achieved a sustained deep molecular response

After discontinuation of Tasigna therapy within the framework of attempting treatment-free remission (TFR), patients may experience musculoskeletal symptoms more frequently than before treatment discontinuation, e.g., myalgia, pain in extremity, arthralgia, bone pain, spinal pain, or musculoskeletal pain.

In a Phase II clinical study with newly diagnosed patients with Ph+ CML-CP (N=190), musculoskeletal symptoms within a year of Tasigna discontinuation were reported in 24.7% vs. 16.3% within the previous year on Tasigna treatment.

In a Phase II clinical study with patients with Ph+ CML-CP on Tasigna and previously treated with imatinib (N=126), musculoskeletal symptoms within a year of discontinuation were reported in 42.1% vs. 14.3% within the previous year on Tasigna treatment.

### Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Tasigna via spontaneous case reports, literature cases, expanded access programs, and clinical studies other than the global registration trials. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to nilotinib exposure.

Frequency not known: Tumour lysis syndrome.

### Pediatric population

The safety of nilotinib in pediatric patients (from 2 to <18 years of age) with Ph+ CML-CP (n=69) has been investigated in two studies (see section CLINICAL STUDIES). In pediatric patients with, the frequency, type and severity of adverse drug reactions observed have been generally consistent with those observed in adults, with the exception of the laboratory abnormalities of hyperbilirubinaemia (Grade 3/4: 13.0%) and transaminase elevation (AST Grade 3/4: 1.4%, ALT Grade 3/4: 8.7%) which were reported at a higher frequency than in adult patients. Bilirubin and hepatic transaminase levels should be monitored during treatment (see section DOSAGE REGIMEN AND ADMINISTRATION)

### INTERACTIONS

Nilotinib is mainly metabolized in the liver with CYP3A4 expected to be the main contributor to the oxidative metabolism. Nilotinib is also a substrate for the multi-drug efflux pump, P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systemically absorbed nilotinib may be influenced by drugs that affect CYP3A4 and/or P-gp.

### Drugs that may increase nilotinib serum concentrations

In a Phase I study of nilotinib given in combination with imatinib (a substrate of P-gp and CYP3A4), both drugs had a slight inhibitory effect on CYP3A4 and/or P-gp. When the two drugs were administered concomitantly, the AUC of imatinib was increased by 18% to 39%, and the AUC of nilotinib was increased by 18% to 40%.

The bioavailability of nilotinib in healthy subjects was increased by 3-fold when co-administered with the strong CYP3A4 inhibitor ketoconazole. Concurrent treatment with strong CYP3A4 inhibitors should therefore be avoided (including but not limited to ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, and telithromycin) (see sections DOSAGE REGIMEN AND ADMINISTRATION AND WARNINGS AND

PRECAUTIONS regarding QT prolongation). Alternative concomitant medications with no or minimal CYP3A4 inhibition should be considered.

#### **Drugs that may decrease nilotinib serum concentrations**

In healthy subjects receiving the CYP3A4 inducer, rifampicin, at 600 mg daily for 12 days, systemic exposure (AUC) to nilotinib was decreased approximately 80%.

Inducers of CYP3A4 activity could increase the metabolism of nilotinib and thereby decrease plasma concentrations of nilotinib. The concomitant administration of medications that induce CYP3A4 (e.g. phenytoin, rifampicin, carbamazepine, phenobarbital, and St. John's Wort) may reduce exposure to nilotinib. In patients for whom CYP3A4 inducers are indicated, alternative agents with less enzyme induction potential should be considered.

Nilotinib has pH-dependent solubility, with lower solubility at higher pH. In healthy subjects receiving esomeprazole at 40 mg once daily for 5 days, gastric pH was markedly increased, but nilotinib absorption was only decreased modestly (27% decrease in  $C_{max}$  and 34% decrease in  $AUC_{0-\infty}$ ). Tasigna may be used concurrently with esomeprazole or other proton pump inhibitors as needed.

In a healthy subjects study, no significant change in nilotinib pharmacokinetics was observed when a single 400 mg dose of Tasigna was administered 10 hours after and 2 hours before famotidine. Therefore, when the concurrent use of an H2 blocker is necessary, it may be administered approximately 10 hours before and approximately 2 hours after the dose of Tasigna.

In the same study as above, administration of an antacid (aluminum hydroxide/magnesium hydroxide/simethicone) 2 hours before or after a single 400 mg dose of Tasigna also did not alter nilotinib pharmacokinetics. Therefore, if necessary, an antacid may be administered approximately 2 hours before or approximately 2 hours after the dose of Tasigna.

#### **Drugs that may have their systemic concentration altered by nilotinib**

*In vitro* nilotinib is identified as a competitive inhibitor of CYP3A4, CYP2C8, CYP2C9, CYP2D6 and UGT1A1, with Ki value being lowest for CYP2C9 ( $Ki=0.13$  microM). Enzyme induction studies indicate that nilotinib can be considered to be an *in vitro* inducer of CYP2B6, CYP2C8 and CYP2C9 activities.

In CML patients, nilotinib administered at 400 mg twice daily for 12 days increased the systemic exposure of oral midazolam (a substrate of CYP3A4) 2.6-fold. Nilotinib is a moderate CYP3A4 inhibitor. As a result, the systemic exposure of other drugs primarily metabolized by CYP3A4 (e.g. certain HMG-CoA reductase inhibitors) may be increased when co-administered with nilotinib. Appropriate monitoring and dose adjustment may be necessary for drugs that are CYP3A4 substrates and have a narrow therapeutic index (including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, sirolimus and tacrolimus) when co-administered with nilotinib.

In healthy subjects, nilotinib at clinically relevant concentrations was not found to alter the pharmacokinetics or pharmacodynamics of warfarin, a sensitive CYP2C9 substrate. Tasigna can be used concurrently with warfarin without increasing the anticoagulant effect.

#### **Anti-arrhythmic medicines and other drugs that may prolong the QT interval**

Concomitant use of anti-arrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol) and other drugs that may prolong the QT interval (including, but not limited to chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil and pimozide) should be avoided (see section WARNINGS AND PRECAUTIONS).

#### **Food interactions**

The absorption and the bioavailability of nilotinib are increased if it is taken with food, resulting in higher serum concentration (see sections DOSAGE REGIMEN AND ADMINISTRATION, WARNINGS AND PRECAUTIONS AND CLINICAL PHARMACOLOGY).

Grapefruit juice and other foods that are known to inhibit CYP3A4 should be avoided at any time.

## **Pregnancy, lactation, females and males of reproductive potential**

### **Pregnancy**

#### **Risk Summary**

Tasigna can cause fetal harm when administered to a pregnant woman. There are no adequate data on the use of Tasigna in pregnant women. Reproductive studies in rats and rabbits have demonstrated that nilotinib induced embryo-toxicity and/or feto-toxicity (following prenatal exposure to nilotinib) at exposures equal to the one achieved in humans at the maximum recommended human dose of 400 mg twice daily. Tasigna should not be used during pregnancy unless necessary. If it is used during pregnancy or if the patient becomes pregnant while taking Tasigna, the patient must be informed of the potential risk to the fetus.

If a woman who is being treated with Tasigna is considering pregnancy, treatment discontinuation may be considered based on the eligibility criteria for discontinuing treatment. There is a limited amount of data on pregnancies in patients while attempting treatment-free remission (TFR). If pregnancy is planned during the TFR phase, the patient must be informed of a potential need to re-initiate Tasigna treatment during pregnancy (see sections DOSAGE REGIMEN AND ADMINISTRATION AND WARNINGS AND PRECAUTIONS)

### **Animal Data**

Nilotinib did not induce teratogenicity, but did show embryo- and fetotoxicity at doses which also showed maternal toxicity. Increased post implantation loss was observed in both the fertility study, with treatment of both males and females, and in the embryotoxicity study with the treatment of females. Embryo-lethality and fetal effects (mainly decreased fetal weights, visceral and skeletal variations) in rats and increased resorption of fetuses and skeletal variations in rabbits were present in the embryo toxicity studies. Exposure to nilotinib in females at No-Observed-Adverse-Effect-Levels (NOAEL) was generally less or equal to that in humans at 800 mg/day.

In a pre- and postnatal study, the oral administration of nilotinib to female rats from day 6 of gestation to day 21 or 22 postpartum resulted in maternal effects (reduced food consumption and lower body weight gains) and longer gestation period at 60 mg/kg. The maternal dose of 60 mg/kg was associated with decreased pup body weight and changes in some physical development parameters (the mean day for pinna unfolding, tooth eruption and eye opening was earlier). The NOAEL in maternal animals and offspring was a maternal dose of 20 mg/kg.

### **Lactation**

#### **Risk Summary**

It is not known whether nilotinib is excreted in human milk. Studies in animals demonstrate that nilotinib is excreted into breast milk. Lactating women should not breast-feed while taking Tasigna and for 2 weeks after the last dose, as a risk to the infant cannot be excluded.

## **Females and males of reproductive potential**

### **Contraception**

#### **Females**

Females of reproductive potential must be advised to use effective method of contraception (methods that result in less than 1% pregnancy rates) while receiving Tasigna and for up to 2 weeks after ending treatment with Tasigna.

### **Infertility**

The effect of nilotinib on male and female fertility is not known. In animal studies no effects on sperm count/motility, and on fertility were noted in male and female rats up to the highest tested dose of approximately 5-fold greater than the recommended dosage for humans.

## **OVERDOSAGE**

Isolated reports of intentional overdose with nilotinib were reported, where an unspecified number of Tasigna capsules were ingested in combination with alcohol and other drugs. Events included neutropenia, vomiting and drowsiness. No ECG changes or hepatotoxicity were reported. Outcomes were reported as recovered.

In the event of overdose, the patient should be observed and appropriate supportive treatment given.

## **CLINICAL PHARMACOLOGY**

### **Mechanism of action (MOA)**

Tasigna is a potent and selective inhibitor of the ABL tyrosine kinase activity of the BCR-ABL oncoprotein both in cell lines and in primary Philadelphia-chromosome positive leukemia cells. The drug binds strongly within the ATP-binding site in such a manner that it is a potent inhibitor of wild-type BCR-ABL and maintains activity against 32/33 imatinib-resistant mutant forms of BCR-ABL. As a consequence of this biochemical activity, nilotinib selectively inhibits the proliferation and induces apoptosis in BCR-ABL dependent cell lines and in primary Philadelphia-chromosome positive leukemia cells derived from CML patients. In murine models of CML, as a single agent nilotinib reduces tumor burden and prolongs survival following oral administration.

### **Pharmacodynamics (PD)**

Tasigna has little or no effect against the majority of other protein kinases examined, including SRC, except for the PDGF, KIT, CSF-1R, DDR and Ephrin receptor kinases which it inhibits at concentrations within the range achieved following oral administration at therapeutic doses recommended for the treatment of CML (see Table 6).

**Table 6 Kinase Profile of Nilotinib (Phosphorylation IC<sub>50</sub> nM)**

BCR-ABL	PDGFR	KIT
20	69	210

### **Pharmacokinetics (PK)**

#### **Absorption**

Peak concentrations of nilotinib are reached 3 hours after oral administration. Nilotinib absorption following oral administration was approximately 30%. The absolute bio-availability of nilotinib has not been determined. As compared to an oral drink solution (pH of 1.2 to 1.3), relative bioavailability of nilotinib capsule is approximately 50%. In healthy volunteers, C<sub>max</sub> and area under the concentration-time curve (AUC) of nilotinib are increased by 112% and 82%, respectively compared to fasting conditions when Tasigna is given with food. Administration of Tasigna 30 minutes or 2 hours after food increased bioavailability of nilotinib by 29% or 15%, respectively (see section DOSAGE REGIMEN AND ADMINISTRATION, WARNINGS AND PRECAUTIONS and INTERACTIONS). Nilotinib absorption (relative bioavailability) may be reduced by approximately 48% and 22% in patients with total gastrectomy and partial gastrectomy, respectively.

#### **Distribution**

Blood-to-plasma ratio of nilotinib is 0.68. Plasma protein binding is approximately 98% on the basis of *in vitro* experiments.

#### **Biotransformation/metabolism**

Main metabolic pathways identified in healthy subjects are oxidation and hydroxylation. Nilotinib is the main circulating component in the serum, primarily metabolized by CYP3A4. None of the metabolites contribute significantly to the pharmacological activity of nilotinib.

#### **Elimination**

After a single dose of radiolabelled nilotinib in healthy subjects, greater than 90% of the dose was eliminated within 7 days mainly in feces. Parent drug accounted for 69% of the dose.

The apparent elimination half-life estimated from the multiple dose PK with daily dosing was approximately 17 hours. Inter-patient variability in nilotinib PK was moderate to high (%CV: 33% to 43%).

#### **Linearity / non-linearity**

Steady-state nilotinib exposure was dose-dependent with less than dose-proportional increases in systemic exposure at dose levels higher than 400 mg given as once daily dosing. Daily systemic exposure to nilotinib of 400 mg twice-daily dosing at steady-state was 35% higher than with 800 mg once-daily dosing. Systemic exposure (AUC) of nilotinib at steady-state at a dose level of 400 mg twice daily was approximately 13.4% higher than with 300 mg twice daily. The average nilotinib trough and peak concentrations over 12 months were

approximately 15.7% and 14.8% higher following 400 mg twice daily dosing compared to 300 mg twice daily. There was no relevant increase in exposure to nilotinib when the dose was increased from 400 mg twice-daily to 600 mg twice-daily.

Steady state conditions were essentially achieved by day 8. An increase in systemic exposure to nilotinib between the first dose and steady-state was approximately 2-fold for the 400 mg once daily dosing and 3.8-fold for the 400 mg twice-daily dosing.

### **Bioavailability/bioequivalence studies**

Single-dose administration of 400 mg of nilotinib, using 2 capsules of 200 mg whereby the content of each capsule was dispersed in one teaspoon of applesauce, was shown to be bioequivalent with a single dose administration of 2 intact capsules of 200 mg.

### **Pediatric population**

Following administration of nilotinib in pediatric patients at 230 mg/m<sup>2</sup> twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg), steady-state exposure and clearance of nilotinib were found to be similar (within 2-fold) to adult patients treated with 400 mg twice daily. The pharmacokinetic exposure of nilotinib following single or multiple doses appeared to be comparable between pediatric patients from 2 years to <10 years and from ≥10 years to <18 years.

## **CLINICAL STUDIES**

### **Newly diagnosed Ph+ CML-CP**

An open label, multicenter, randomized Phase III study was conducted to determine the efficacy of Tasigna versus imatinib in adult patients with cytogenetically confirmed newly diagnosed Ph+ CML-CP. Patients were within six months of diagnosis and were previously untreated for CML-CP, except for hydroxyurea and/or anagrelide. In addition, patients were stratified according to Sokal risk score at time of diagnosis.

Efficacy was based on a total of 846 patients (283 patients in the imatinib 400 mg once daily group, 282 patients in the nilotinib 300 mg twice daily group, 281 patients in the nilotinib 400 mg twice daily group).

Baseline characteristics were well balanced between the three groups. Median age was 46 years in the imatinib group and 47 years in both nilotinib groups, with 12.4%, 12.8% and 10.0% were ≥65 years of age in imatinib, nilotinib 300 mg twice daily and nilotinib 400 mg twice daily treatment groups, respectively. There were slightly more male than female patients in all groups (55.8%, 56.0% and 62.3% in imatinib, nilotinib 300 mg twice daily and nilotinib 400 mg twice daily, respectively). More than 60% of all patients were Caucasian, and 25% were Asian.

The primary data analysis time point was when all 846 patients completed 12 months of treatment (or discontinued earlier). Subsequent analyses reflect when patients completed 24, 36, 48 and 60 months of treatment (or discontinued earlier). The median time on treatment was approximately 60 months in all three treatment groups. The median actual dose intensity was 400 mg/day in the imatinib group, 593 mg/day in the nilotinib 300 mg twice daily group and 773 mg/day in the nilotinib 400 mg twice daily group. This study is on-going.

### **Major molecular response (MMR)**

The primary efficacy variable was MMR at 12 months after the start of study medication. MMR was defined as ≤0.1% BCR-ABL/ABL % by international scale measured by RQ-PCR, which corresponds to a ≥3 log reduction of BCR-ABL transcript from standardized baseline.

The primary efficacy endpoint, MMR rate at 12 months was statistically significantly superior in the nilotinib 300 mg twice daily group compared to the imatinib 400 mg once daily group (44.3% vs. 22.3%, p<0.0001). The rate of MMR at 12 months, was also statistically significantly higher in the nilotinib 400 mg twice daily group compared to the imatinib 400 mg once daily group (42.7% vs. 22.3%, p<0.0001), Table 7.

At the nilotinib recommended dose of 300 mg twice daily, the rates of MMR at 3, 6, 9 and 12 months were 8.9%, 33.0%, 43.3% and 44.3%. In the nilotinib 400 mg twice daily group, the rates of MMR at 3, 6, 9 and 12 months were 5.0%, 29.5%, 38.1% and 42.7%. In the imatinib 400 mg once daily group, the rates of MMR at 3, 6, 9 and 12 months were 0.7%, 12.0%, 18.0% and 22.3%.

The MMR rates at 12, 24, 36, 48 and 60 months are presented in Table 7.

**Table 7** MMR rate

	Tasigna 300 mg twice daily N=282 n (%)	Tasigna 400 mg twice daily N=281 n (%)	Imatinib 400 mg once daily N=283 n (%)
<b>MMR at 12 months</b>	125(44.3) <sup>1</sup> [38.4,50.3]	120(42.7) <sup>1</sup> [36.8,48.7]	63(22.3) [17.6, 27.6]
<b>MMR at 24 months</b>	174 (61.7) <sup>1</sup> [55.8,67.4]	166 (59.1) <sup>1</sup> [53.1,64.9]	106 (37.5) [31.8,43.4]
<b>MMR at 36 months<sup>2</sup></b>	165 (58.5) <sup>1</sup> [52.5,64.3]	161 (57.3) <sup>1</sup> [51.3,63.2]	109 (38.5) [32.8,44.5]
<b>MMR at 48 months<sup>3</sup></b>	169 (59.9) <sup>1</sup> [54.0,65.7]	155 (55.2) [49.1,61.1]	124 (43.8) [38.0,49.8]
<b>MMR at 60 months<sup>4</sup></b>	177 (62.8) [56.8,68.4]	172 (61.2) [55.2,66.9]	139 (49.1) [43.2,55.1]

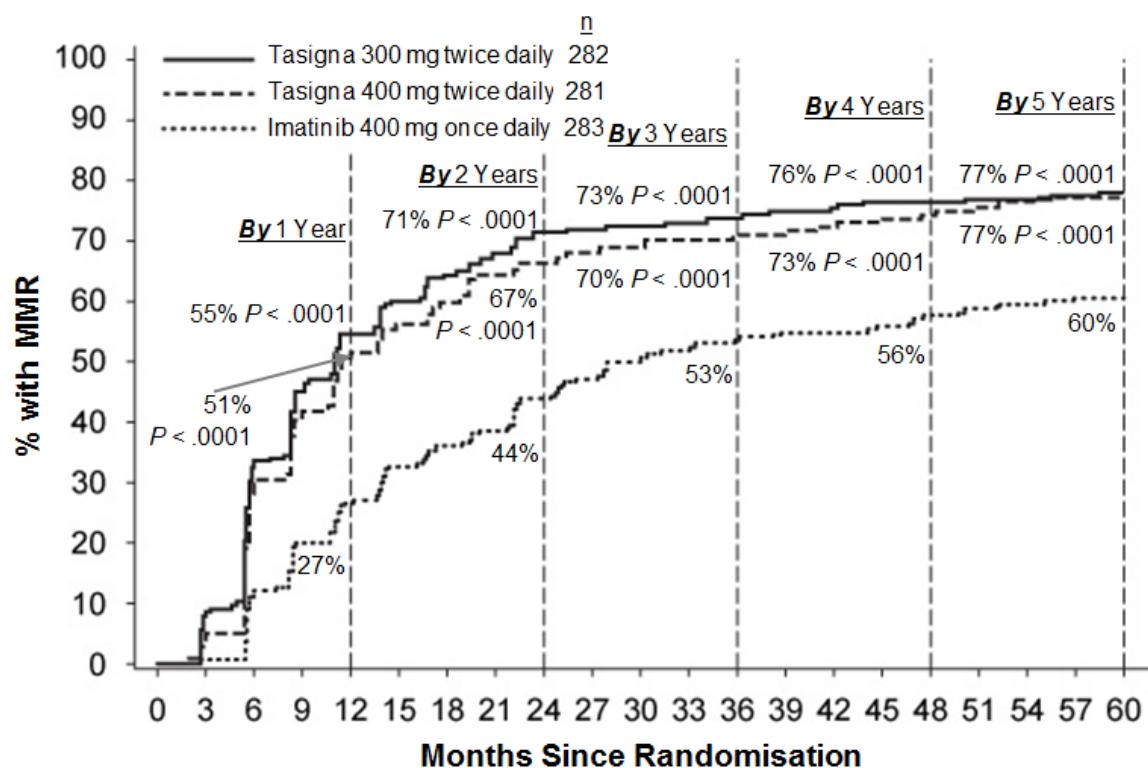
<sup>1</sup> CMH test p-value for response rate (vs. Imatinib 400 mg) <0.0001,

<sup>2</sup> Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 199 (35.2%) of all patients were not evaluable for MMR at 36 months (87 in the nilotinib 300 mg BID group and 112 in the imatinib group) due to missing/unevaluable PCR assessments (n=17), atypical transcripts at baseline (n=7), or discontinuation prior to the 36-month time point (n=175).

<sup>3</sup> Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 305 (36.1%) of all patients were not evaluable for MMR at 48 months (98 in the nilotinib 300 mg BID group, 88 in the nilotinib 400 mg BID group and 119 in the imatinib group) due to missing/unevaluable PCR assessments (n=18), atypical transcripts at baseline (n=8), or discontinuation prior to the 48-month time point (n=279).

<sup>4</sup> Only patients who were in MMR at a specific time point are included as responders for that time point. A total of 322 (38.1%) of all patients were not evaluable for MMR at 60 months (99 in the nilotinib 300mg BID group, 93 in the nilotinib 400 mg BID group and 130 in the imatinib group) due to missing/unevaluable PCR assessments (n=9), atypical transcripts at baseline (n=8), or discontinuation prior to the 60-month time point (n=305).

MMR rates by different time points (including patients who achieved MMR at or before those time points as responders) are presented in the cumulative incidence of MMR (Figure 1)

**Figure 1****Cumulative Incidence of MMR**

For all Sokal risk groups, the MMR rates at all time points remained consistently higher in the two nilotinib groups than in the imatinib group.

In a retrospective analysis, 91% (234/258) of patients on nilotinib 300 mg twice daily achieved BCR-ABL levels  $\leq 10\%$  at 3 months of treatment compared to 67% (176/264) of patients on imatinib 400 mg once daily. Patients with BCR-ABL levels  $\leq 10\%$  at 3 months of treatment show a greater overall survival at 60 months compared to those who did not achieve this molecular response level (97% vs. 82% respectively [p=0.0116]).

Based on the Kaplan-Meier analyses of time to first MMR among all patients the probability of achieving MMR at different time points were higher in both nilotinib groups compared to the imatinib group (HR=2.20 and stratified log-rank p<0.0001 between nilotinib 300 mg twice daily and imatinib, HR=1.88 and stratified log-rank p<0.0001 between nilotinib 400 mg twice daily and imatinib).

The proportions of patients who had a molecular response of  $\leq 0.01\%$  and  $\leq 0.0032\%$  by International Scale (IS) at different time-points is presented in Table 8 and the proportion of patients who had a molecular response of  $\leq 0.01\%$  and  $\leq 0.0032\%$  by IS-by different time-points are presented in Figure 2 and 3. Molecular responses of  $\leq 0.01\%$  and  $\leq 0.0032\%$  by IS corresponds to a  $\geq 4$  log reduction and  $\geq 4.5$  log reduction, respectively, of BCR-ABL transcripts from a standardized baseline.

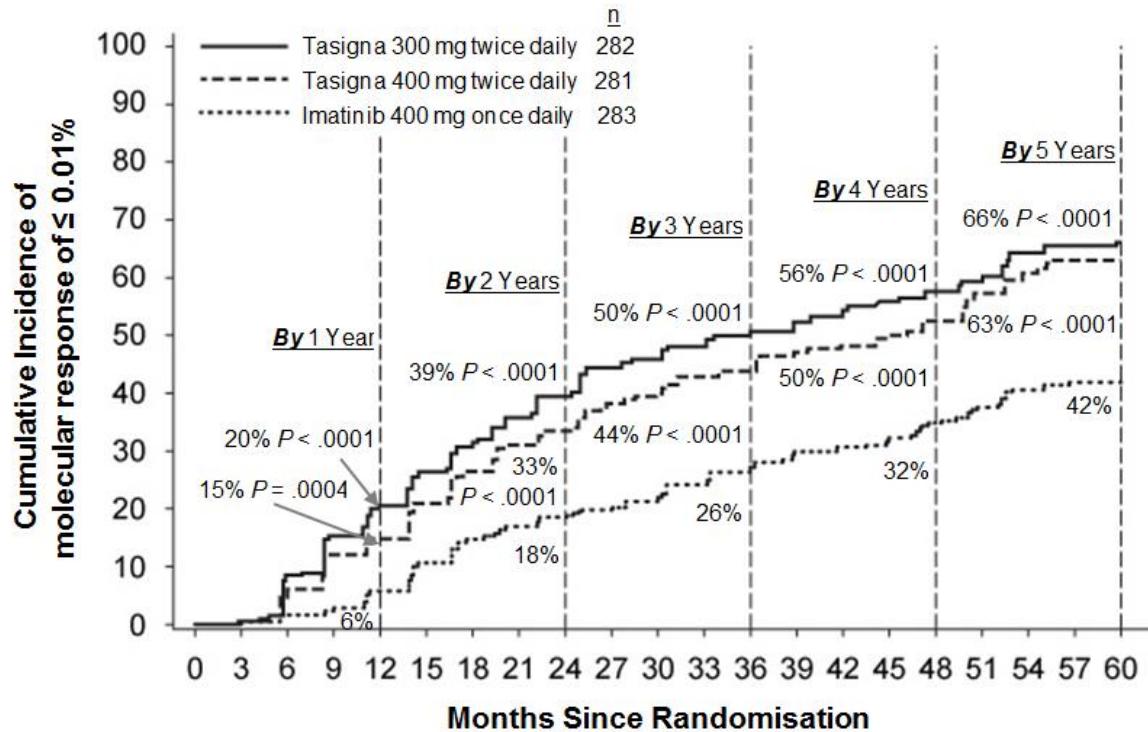
**Table 8** Proportions of patients who had molecular response of  $\leq 0.01\%$  (4 log reduction and  $\leq 0.0032\%$  (4.5 log reduction)

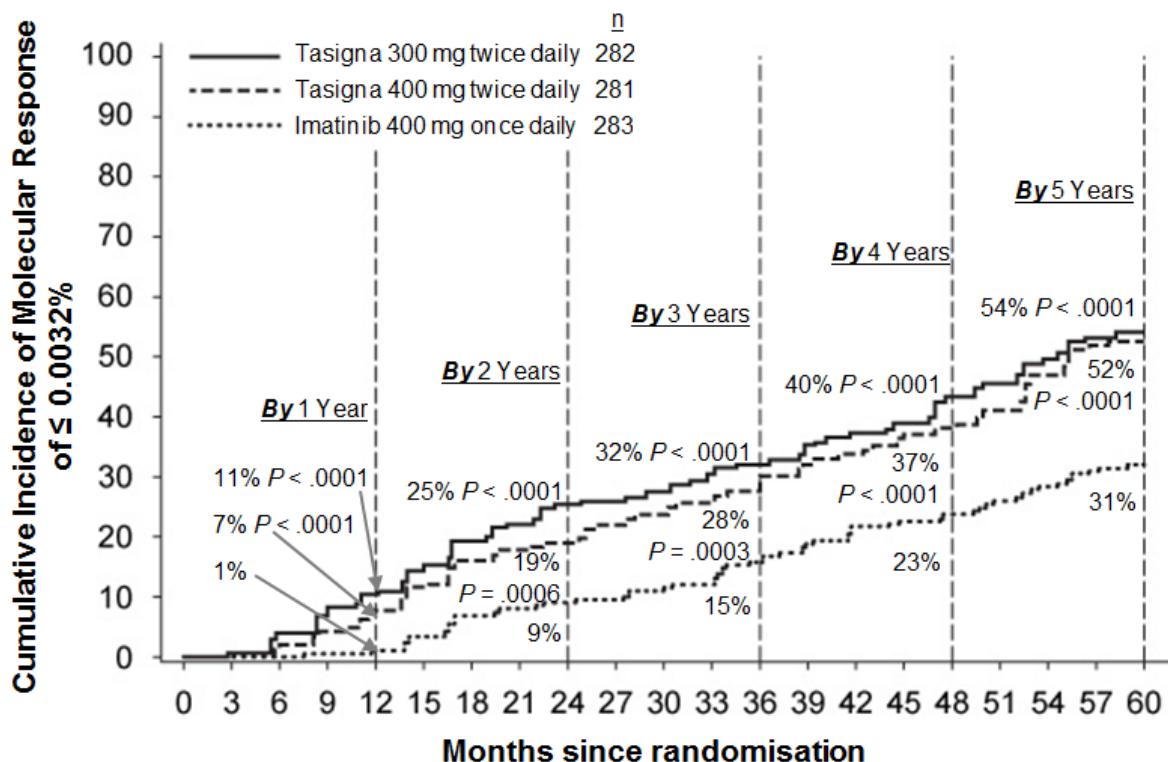
	Tasigna 300 mg twice daily N=282		Tasigna 400 mg twice daily N=281		Imatinib 400 mg once daily N=283	
	(%)		(%)		(%)	
	$\leq 0.01\%$	$\leq 0.0032\%$	$\leq 0.01\%$	$\leq 0.0032\%$	$\leq 0.01\%$	$\leq 0.0032\%$
At 12 months	11.7	4.3	8.5	4.6	3.9	0.4

At 24 months	24.5	12.4	22.1	7.8	10.2	2.8
At 36 months	29.4	13.8	23.8	12.1	14.1	8.1
At 48 months	33.0	16.3	29.9	17.1	19.8	10.2
At 60 months	47.9	32.3	43.4	29.5	31.1	19.8

**Figure 2**

**Cumulative incidence of molecular response of  $\leq 0.01\%$  (4-log reduction)**



**Figure 3****Cumulative incidence of molecular response of  $\leq 0.0032\%$  (4.5 log reduction)**

#### Duration of MMR

Based on Kaplan-Meier estimates of the duration of first MMR, the proportions of patients who were maintaining response after 60 months among patients who achieved MMR were 93.4% (95% CI: 89.9% to 96.9%) in the nilotinib 300 mg twice daily group, 92.0% (95% CI: 88.2% to 95.8%) in the nilotinib 400 mg twice daily group and 89.1% (95% CI: 84.2% to 94.0%) in the imatinib 400 mg once daily group.

#### Complete Cytogenetic response (CCyR)

CCyR was defined as 0% Ph+ metaphases in the bone marrow based on a minimum of 20 metaphases evaluated. CCyR rate by 12 months (includes patients who achieved CCyR at or before the 12 month time point as responders) was statistically higher for both the nilotinib 300 mg twice daily and 400 mg twice daily groups compared to imatinib 400 mg once daily group, Table 9.

CCyR rate by 24 months (includes patients who achieved CCyR at or before the 24 month time point as responders) was statistically higher for both the nilotinib 300 mg twice daily and 400 mg twice daily groups compared to imatinib 400 mg once daily group.

**Table 9** CCyR rate

	Tasigna 300 mg twice daily N=282 n (%)	Tasigna 400 mg twice daily N=281 n (%)	Imatinib 400 mg once daily N=283 n (%)
<b>By 12 months</b>			
Complete Cytogenetic Response	226 (80.1)	219 (77.9)	184 (65.0)
95% CI for response	[75.0,84.6]	[72.6,82.6]	[59.2,70.6]
CMH test p-value for response rate (vs. Imatinib 400 mg)	<0.0001	0.0005	
<b>By 24 months</b>			

<b>Complete Cytogenetic Response</b>	245 (86.9%)	238 (84.7%)	218 (77.0%)
95% CI for response	[82.4, 90.6]	[79.9, 88.7]	[71.7, 81.8]
<b>CMH test p-value for response rate (vs. Imatinib 400 mg)</b>	0.0018	0.0160	

### Duration of CCyR

Based on Kaplan-Meier estimates, the proportions of patients who were maintaining response after 60 months among patients who achieved CCyR were 99.1% (95% CI: 97.9% to 100%) in the nilotinib 300 mg twice daily group, 98.7% (95% CI: 97.1% to 100%) in the nilotinib 400 mg twice daily group and 97.0% (95% CI: 94.7% to 99.4%) in the imatinib 400 mg once daily group.

### Progression to AP/BC on treatment

Progression to AP/BC on treatment is defined as the time from the date of randomization to the first documented disease progression to AP/BC or CML-related death. Overall by the cut-off date, 17 patients progressed to AP or BC on treatment (2 in the nilotinib 300 mg twice daily group, 3 in the nilotinib 400 mg twice daily group and 12 in the imatinib 400 mg once daily group). The estimated rates of patients free from progression to AP or BC at 60 months were 99.3%, 98.7% and 95.2%, respectively (HR=0.1599 and stratified log-rank p=0.0059 between nilotinib 300 mg BID and imatinib, HR=0.2457 and stratified log-rank p=0.0185 between nilotinib 400 mg BID and imatinib). No new events of progression to AP/BC were reported on-treatment since the 2-year analysis.

Including clonal evolution as a criterion for progression, a total of 25 patients progressed to AP or BC on treatment by the cut-off date (3 in the nilotinib 300 mg twice daily group, 5 in the nilotinib 400 mg twice daily group and 17 in the imatinib 400 mg once daily group). The estimated rates of patients free from progression to AP or BC including clonal evolution at 60 months were 98.7%, 97.9% and 93.2%, respectively (HR=0.1626 and stratified log-rank p=0.0009 between nilotinib 300 mg BID and imatinib, HR = 0.2848 and stratified log-rank p=0.0085 between nilotinib 400 mg BID and imatinib).

### Overall survival (OS)

A total of 50 patients died during treatment or during the follow-up after discontinuation of treatment (18 in the nilotinib 300 mg twice daily group, 10 in the nilotinib 400 mg twice daily group and 22 in the imatinib 400 mg once daily group). Twenty-six (26) of these 50 deaths were related to CML (6 in the nilotinib 300 mg twice daily group, 4 in the nilotinib 400 mg twice daily group and 16 in the imatinib 400 mg once daily group). The estimated rates of patients alive at 60 months were 93.7%, 96.2% and 91.7%, respectively (HR=0.8026 and stratified log-rank p = 0.4881 between nilotinib 300 mg twice daily and imatinib, HR=0.4395 and stratified log-rank p = 0.0266 between nilotinib 400 mg twice daily and imatinib). Considering only CML-related deaths as events, the estimated rates of OS at 60 months were 97.7%, 98.5% and 93.8%, respectively (HR=0.3673 and stratified log-rank p = 0.0292 between nilotinib 300 mg twice daily and imatinib, HR=0.2411 and stratified log-rank p = 0.0057 between nilotinib 400 mg twice daily and imatinib).

### Switch to Tasigna treatment in adult patients with Ph+ CML-CP who have not achieved a molecular response greater than or equal to a 4.5-log reduction with imatinib treatment

In an open-label, multicenter, randomized Phase III study, 207 adult patients with Ph+ CML-CP who received treatment with imatinib for at least 2 years, with no permanent imatinib dose adjustment within 6 months and no major toxicity within 3 months of study entry were enrolled in the study. Patients were randomized 1:1 either to receive Tasigna 400 mg twice daily (n=104) or to continue treatment with imatinib at the same dose (400 mg or 600 mg once daily) as administered prior to randomization (n=103). Randomization was stratified by duration of prior treatment with imatinib and duration of prior interferon use. The median time on treatment (from first day of treatment to last day of randomized treatment) at cut-off was 47.2 months in the Tasigna treatment arm, and 37.0 months and 26.7 months in the 400 mg and 600 mg dose cohorts of the imatinib arm, respectively.

The two treatment arms were well balanced with respect to demographic and baseline characteristics (including BCR-ABL transcript levels at study entry). Median age was 46 years in the Tasigna arm and 52 years in the imatinib arm, with 13.5% and 13.6% of patients aged  $\geq 65$  years in the Tasigna and imatinib treatment arms, respectively. There were more male (68.3% in the Tasigna treatment arm and 63.1% in the imatinib treatment arm) than female patients. More than 80% of all patients were Caucasians. Up to the cut-off date, the median actual dose intensity was 775.7 mg/day in the Tasigna treatment arm and 400 mg/day and 600 mg/day in the two dose cohorts of the imatinib treatment arm, respectively.

The primary endpoint of the study was the rate of confirmed best cumulative complete molecular response (CMR) within the first year of study therapy with Tasigna or imatinib. The rate of confirmed best cumulative CMR during the first 12 months was 12.5% in the Tasigna arm and 5.8% in the imatinib arm. The primary endpoint did not reach statistical significance at the early 12-month time point ( $p=0.1083$ ), with an odds ratio (OR) of 2.096 in favor of Tasigna.

Longer-term follow-up of the primary outcome variable at 48-months was a secondary endpoint. Analyses conducted to assess the achievement of different levels of molecular response up to crossover in patients without the corresponding response at baseline showed that switching from imatinib to Tasigna was associated with a clinically meaningful increase in the numbers of patients attaining MMR, MR4.5, and CMR under their randomized treatment at Month 48 (see Table 10)

**Table 10 Rate of best cumulative molecular response up to crossover by baseline molecular response status**

	TASIGNA N=104 n (%)	Imatinib N=103 n (%)
Number of patients with MMR at baseline	79 (76.0)	74 (71.8)
Number of patients without MMR at baseline	24 (23.1)	28 (27.2)
MMR by 12 months	18 (75.0)	10 (35.7)
MMR by 24 months	20 (83.3)	14 (50.0)
MMR by 36 months	21 (87.5)	15 (53.6)
MMR by 48 months	21 (87.5)	15 (53.6)
MR4.5 by 48 months	8 (33.3)	1 (3.6)
CMR by 48 months	7 (29.2)	1 (3.6)
Number of patients with MR4.5 at baseline	5 (4.8)	6 (5.8)
Number of patients without MR4.5 at baseline	98 (94.2)	96 (93.2)
MR4.5 by 12 months	32 (32.7)	13 (13.5)
MR4.5 by 24 months	42 (42.9)	20 (20.8)
MR4.5 by 36 months	46 (46.9)	25 (26.0)
MR4.5 by 48 months	51 (52.0)	27 (28.1)
CMR by 48 months	44 (44.9)	18 (18.8)
Number of patients with CMR at baseline	2 (1.9)	2 (1.9)
Number of patients without CMR at baseline	101 (97.1)	100 (97.1)
CMR by 12 months	21 (20.8)	10 (10.0)
CMR by 24 months	33 (32.7)	18 (18.0)
CMR by 36 months	41 (40.6)	20 (20.0)
CMR by 48 months	45 (44.6)	20 (20.0)

#### **Resistant or intolerant Ph+ CML**

An open-label multicenter Phase II study was conducted to determine the efficacy of Tasigna (400 mg twice daily) in adult patients with imatinib resistant or intolerant CML with separate treatment arms for chronic and accelerated phase disease. Efficacy was based on 321 CP patients and 137 AP patients enrolled. Median duration of treatment was 561 days and 264 days, respectively (see Table 11). Tasigna was administered on a continuous basis, (twice daily 2 hours after a meal and no additional food for at least one hour) unless there was evidence of inadequate response or disease progression. Dose escalation to 600 mg twice daily was allowed.

**Table 11 Duration of Exposure with Tasigna**

	<b>Chronic Phase N = 321</b>	<b>Accelerated Phase N = 137</b>
Median duration of therapy in days (25 <sup>th</sup> – 75 <sup>th</sup> percentiles)	561 (196-852)	264 (115-595)

Resistance to imatinib included failure to achieve a complete hematologic response (by 3 months), cytogenetic response (by 6 months) or major cytogenetic response (by 12 months) or progression of disease after a previous cytogenetic or hematologic response. Imatinib intolerance included patients who discontinued imatinib because of toxicity and were not in major cytogenetic response at time of study entry.

Overall, 73% of patients were imatinib-resistant while 27% were imatinib-intolerant. The majority of patients had a long history of CML that included extensive prior treatment with other antineoplastic agents such as imatinib, hydroxyurea, interferon, and some that had even failed stem cell transplant (Table 12). The median highest prior imatinib dose had been 600 mg/day for CP and AP patients, and the highest prior imatinib dose was ≥600 mg/day in 74% of all patients with 40% of patients receiving imatinib doses ≥800 mg/day.

**Table 12 CML Disease History Characteristics**

	<b>Chronic Phase (n = 321)</b>	<b>Accelerated Phase (n = 137)*</b>
Median time since diagnosis in months (range)	58 (5-275)	71 (2-298)
Imatinib		
Resistant	226 (70%)	109 (80%)
Intolerant without MCyR	95 (30%)	27 (20%)
Median time of imatinib treatment in days (25 <sup>th</sup> – 75 <sup>th</sup> percentiles)	976 (519 - 1,488)	857 (424 - 1,497)
Prior Hydroxyurea	83%	91%
Prior Interferon	58%	50%
Prior organ transplant	7%	8%

\* One patient had missing information for imatinib-resistant/intolerant status

The primary endpoint in the CP patients was major cytogenetic response (MCyR), defined as elimination (CCyR, complete cytogenetic response) or significant reduction to <35% Ph+ metaphases (partial cytogenetic response) of Ph+ hematopoietic cells. Complete hematologic response (CHR) in CP patients was evaluated as a secondary endpoint. The primary endpoint in the AP patients was overall confirmed hematologic response (HR), defined as either a complete hematologic response, no evidence of leukemia or return to chronic phase.

**Chronic Phase:** The MCyR rate in 321 CP patients was 59%. Most responders achieved their MCyR rapidly within 3 months (median 2.8 months) of starting Tasigna treatment and these were sustained. The CCyR rate was 44%. The median time to achieve CCyR was just past 3 months (median 3.3 months). Of the patients who achieved MCyR, 77% (95% CI: 71% to 84%) were maintaining response at 24 months. Median duration of MCyR has not been reached. Of the patients who achieved CCyR, 84% (95% CI: 77% to 91%) were maintaining response at 24 months. Median duration of CCyR has not been reached. Patients with a CHR at baseline achieved a MCyR faster (1.4 vs. 2.8 months). Of CP patients without a baseline CHR, 76% achieved a CHR, median time to CHR was 1 month and median duration of CHR has not been reached.

The estimated 24-month overall survival rate in CML -CP patients was 87%.

**Accelerated Phase:** The overall confirmed HR rate in 137 AP patients was 55%. Most responders achieved a HR early with Tasigna treatment (median 1.0 months) and these have been durable (median duration of confirmed

HR was 21.5 months). Of the patients who achieved HR, 49% (95% CI: 35% to 62%) were maintaining response at 24 months. MCyR rate was 32% with a median time to response of 2.8 months. Of the patients who achieved MCyR, 66% (95% CI: 50% to 82%) were maintaining response at 24 months. Median duration of MCyR has not been reached. The rates of response for the two treatment arms are reported in Table 13.

The estimated 24-month overall survival rate in CML -AP patients was 70%.

**Table 13 Response rate in CML**

<b>(Best Response Rate)</b>	<b>Chronic Phase</b>			<b>Accelerated Phase</b>		
	<b>Intolerant (n = 95)</b>	<b>Resistant (n = 226)</b>	<b>Total (n = 321)</b>	<b>Intolerant (n = 27)</b>	<b>Resistant (n = 109)</b>	<b>Total* (n = 137)</b>
<b>Hematologic Response (%)</b>						
Overall (95%CI)	-	-	-	56 (35-75)	55 (45-65)	55 (47-64)
Complete	90 (79-97)	72 (64-79)	76 <sup>1</sup> (70-82)	37	30	31
NEL	-	-	-	15	11	12
Return to CP	-	-	-	4	14	12
<b>Cytogenetic Response (%)</b>						
Major (95%CI)	66 (56-76)	56 (49-63)	59 (54-65)	41 (22-61)	30 (22-40)	32 (24-41)
Complete	51	41	44	30	19	21
Partial	16	15	15	11	11	11

NEL = no evidence of leukemia/marrow response

<sup>1</sup>- 114 CP patients had a CHR at baseline and were therefore not assessable for complete hematologic response

\* One patient had missing information for imatinib-resistant/tolerant status

Separate treatment arms were also included in the Phase II study to study Tasigna in a group of CP and AP patients who had been extensively pre-treated with multiple therapies including a tyrosine kinase inhibitor agent in addition to imatinib. Of these patients 30/36 (83%) were treatment-resistant. In 22 CP patients evaluated for efficacy Tasigna induced a 32% MCyR rate and a 50% CHR rate. In 11 AP patients evaluated for efficacy, treatment induced a 36% overall HR rate.

After imatinib failure, 24 different BCR-ABL mutations were noted in 42% of chronic phase and 54% of accelerated phase CML patients who were evaluated for mutations. Tasigna demonstrated efficacy in patients harboring a variety of BCR-ABL mutations associated with imatinib resistance, except T315I.

#### **Treatment discontinuation in newly diagnosed Ph+ CML-CP adult patients who have achieved a sustained deep molecular response**

In an open-label, multicenter, single-arm study, 215 adult patients with Ph+ CML-CP treated with Tasigna in first-line for ≥2 years who achieved MR4.5 as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 215 patients, 190 patients (88.4%) entered the “Treatment-free Remission” (TFR) phase after achieving a sustained deep molecular response during the consolidation phase, defined by the following criteria:

- The 4 last quarterly assessments (taken every 12 weeks) were at least MR4.0 (BCR-ABL / ABL ≤0.01% IS), and maintained for 1 year
- The last assessment being MR4.5 (BCR-ABL / ABL ≤0.0032% IS)
- No more than two assessments falling between MR4.0 and MR4.5 (0.0032% IS <BCR-ABL / ABL ≤0.01% IS).

In the set of patients who entered the TFR phase, the median age was 55 years. The proportion of female patients was 49.5%, and 21.1% of the patients were ≥65 years of age. The median actual dose intensity during the 52-week Tasigna consolidation phase was 600.0 mg/day.

BCR-ABL levels were monitored every 4 weeks during the first 48 weeks of the TFR phase. Monitoring frequency was intensified to every 2 weeks upon the loss of MR4.0. Biweekly monitoring ended at one of the following time points:

- Loss of MMR requiring patient to re-initiate Tasigna treatment
- When the BCR-ABL levels returned to a range between MR4.0 and MR4.5
- When the BCR-ABL levels remained lower than MMR for 4 consecutive measurements (8 weeks from initial loss of MR4.0).

Any patient with loss of MMR during the TFR phase re-initiated Tasigna treatment at 300 mg twice daily or at a reduced dose level of 400 mg once daily if required from the perspective of tolerance, within 5 weeks after the collection date of the blood sample demonstrating loss of MMR. Patients who required re-initiation of Tasigna treatment were monitored for BCR-ABL levels every 4 weeks for the first 24 weeks and then every 12 weeks thereafter in patients who regained MMR.

The primary endpoint was the percentage of patients who were in MMR at 48 weeks after starting the TFR phase (considering any patient who required re-initiation of treatment as non-responder). Of the 190 patients who entered the TFR phase, 98 patients (51.6% [95% CI: 44.2, 58.9]) were in MMR in the TFR phase at 48 weeks.

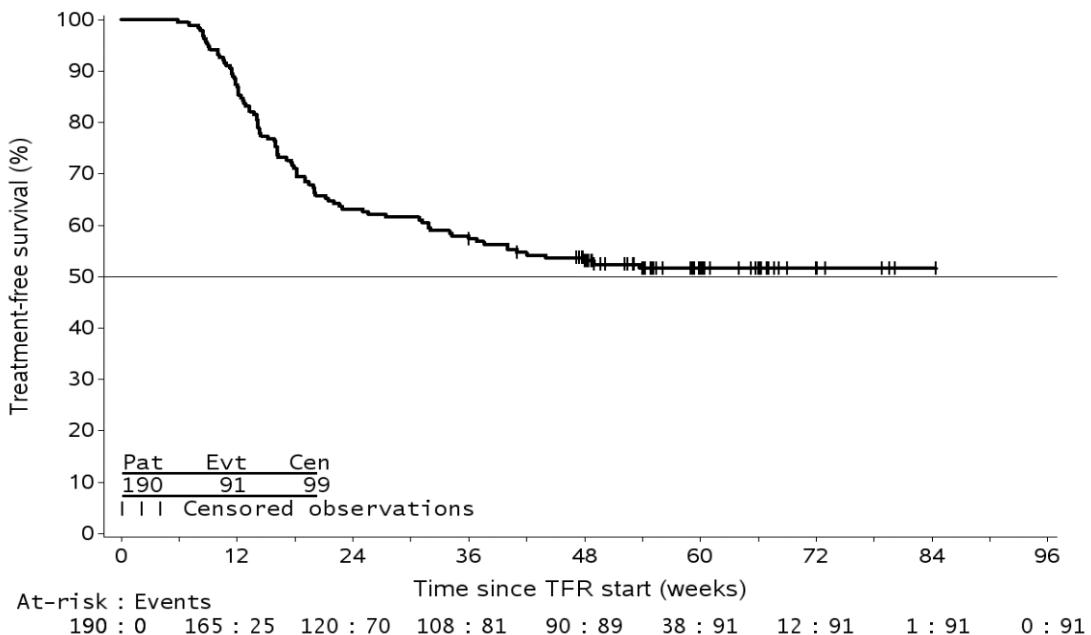
Eighty-eight patients (46.3%) discontinued from the TFR phase due to loss of MMR, and 1 (0.5%), 1 (0.5%), and 3 patients (1.6%) due to death from unknown cause, physician decision, and subject decision, respectively. Among the 88 patients who discontinued the TFR phase due to loss of MMR, 86 patients restarted Tasigna treatment and 2 patients permanently discontinued from the study.

Of the 86 patients who restarted treatment due to loss of MMR in the TFR phase, 85 patients (98.8%) regained MMR, (one patient discontinued study permanently due to subject decision) and 76 patients (88.4%) regained MR4.5 by the time of the cut-off date.

The Kaplan-Meier (KM) estimated median time on Tasigna to regain MMR and MR4.5 was 7.9 weeks (95% CI: 5.1, 8.0) and 13.1 weeks (95% CI: 12.3, 15.7), respectively. The KM estimated MMR rate at 24 weeks of re-initiation was 98.8% (95% CI: 94.2, 99.9). The KM estimated MR4.5 rate at 24 weeks of re-initiation was 90.9% (95% CI: 83.2, 96.0).

Among the 190 patients in the TFR phase, 99 patients (52.1%) did not have a treatment-free survival (TFS) event on or before the 48 month cut-off date, and were censored at the date of their last assessment prior to cut-off. The KM estimate of median TFS has not yet been reached (Figure 4).

**Figure 4 Kaplan-Meier estimate of treatment-free survival after start of TFR (Full Analysis Set)**



#### Treatment discontinuation in Ph+ CML-CP adult patients who have achieved a sustained deep molecular response on Tasigna following prior imatinib therapy

In an open-label, multicenter, single-arm study, 163 adult patients with Ph+ CML-CP taking tyrosine kinase inhibitors (TKIs) for  $\geq 3$  years (imatinib as initial TKI therapy for more than 4 weeks without documented MR4.5 on imatinib at the time of switch to Tasigna, then switched to Tasigna for at least two years), and who achieved

MR4.5 on Tasigna treatment as measured with the MolecularMD MRDx™ BCR-ABL Test were enrolled to continue Tasigna treatment for an additional 52 weeks (Tasigna consolidation phase). Of the 163 patients, 126 patients (77.3%) entered the TFR phase after achieving a sustained deep molecular response during the consolidation phase, defined by the following criterion:

- The 4 last quarterly assessments (taken every 12 weeks) showed no confirmed loss of MR4.5 (BCR-ABL/ABL  $\leq 0.0032\%$  IS) during 1 year.

The median age of the patients who entered the TFR phase was 56 years. The proportion of female patients was 55.6%, and 27.8% of the patients were  $\geq 65$  years of age. The median actual dose intensity during the 52-week Tasigna consolidation phase was 771.8 mg/day with 52.4% and 29.4% of patients receiving a daily Tasigna dose of 800 mg and 600 mg just before entry into the TFR phase, respectively.

Patients who entered the TFR phase but experienced two consecutive measurements of BCR-ABL/ABL  $> 0.01\%$  IS were considered having a confirmed loss of MR4.0, triggering re-initiation of Tasigna treatment. Patients with loss of MMR in the TFR phase immediately restarted Tasigna treatment without confirmation. All patients who restarted Tasigna therapy had BCR-ABL transcript levels monitored every 4 weeks for the first 24 weeks, then once every 12 weeks.

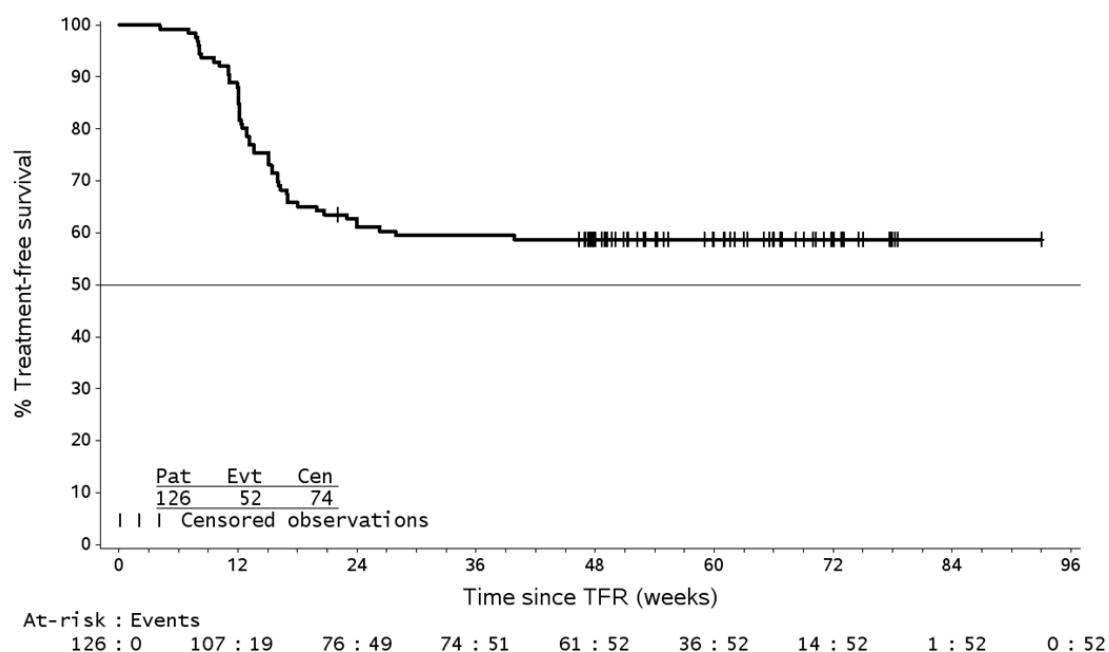
The primary endpoint was defined as the proportion of patients without confirmed loss of MR4.0 or loss of MMR within 48 weeks following discontinuation of Tasigna therapy. Of the 126 patients who entered the TFR phase, 73 patients (57.9%, [95% CI: 48.8, 66.7]) had no loss of MMR, no confirmed loss of MR4.0, and no re-initiation of Tasigna therapy within 48 weeks after the start of the TFR phase.

Among the 53 patients who discontinued from the TFR phase due to confirmed loss of MR4.0 or loss of MMR, 51 patients restarted Tasigna therapy and 2 patients permanently discontinued from the study. Of the 51 patients who restarted Tasigna treatment due to confirmed loss of MR4.0 or loss of MMR in the TFR phase, 48 patients (94.1%) regained MR4.0 and 3 patients (5.9%) did not regain MR4.0. Forty-seven patients (92.2%) regained MR4.5 and 4 patients (7.8%) did not regain MR4.5 by the time of the cut-off date.

The Kaplan-Meier (KM) estimated median time on Tasigna to regain MR4.0 and MR4.5 was 12.0 weeks (95% CI: 8.3, 12.7) and 13.1 weeks (95% CI: 12.4, 16.1), respectively. The KM estimated rate of MR4.0 at 48 weeks of re-initiation was 100.0%. (95% CI: not estimated). The KM estimated rate of MR4.5 at 48 weeks of re-initiation was 94.8% (95% CI: 85.1, 99.0).

Among the 126 patients in the TFR phase, 74 patients (58.7%) did not have a treatment-free survival (TFS) event on or before the 48-month cut-off date, and were censored at the date of their last assessment prior to cut-off. The other 52 patients had a TFS event (18 patients had confirmed loss of MR4.0, and 34 patients lost MMR). The median TFS has not yet been reached (Figure 5).

**Figure 5 Kaplan-Meier estimate of treatment-free survival after start of TFR (full analysis set)**



### Pediatric patients with newly diagnosed Ph+ CML-CP or resistant or intolerant Ph+ CML-CP

The safety and efficacy of nilotinib in pediatric patients with Ph+ CML-CP have been investigated in two studies. A total of 69 pediatric patients (from 2 to <18 years of age) with either newly diagnosed Ph+ CML-CP (n=25) or imatinib/dasatinib resistant or intolerant imatinib-Ph+ CML-CP (n=44) received nilotinib treatment at a dose of 230 mg/m<sup>2</sup> twice daily, rounded to the nearest 50 mg dose (to a maximum single dose of 400 mg).

In the pooled CML patient population, the median actual dose intensity was 435.5 mg/m<sup>2</sup>/day (range: 149 to 517 mg/m<sup>2</sup>/day), and the median relative dose intensity was 94.7% (range: 32 to 112%). Forty patients (58.0%) had relative dose intensity superior to 90%. The median time on treatment with nilotinib was 13.80 months (range: 0.7 to 30.9 months).

In the resistant or intolerant CML patients, the major molecular response (MMR; BCR-ABL/ABL ≤0.1% IS) rate was 40.9% (95% CI: 26.3, 56.8) at 12 cycles, with 18 patients being in MMR. In the newly diagnosed CML patients, the MMR rate was 60.0% (95% CI: 38.7, 78.9) at 12 cycles, with 15 patients achieving MMR. In resistant or intolerant CML patients, the cumulative MMR rate was 47.7% by cycle 12. In newly diagnosed CML patients, the cumulative MMR rate was 64.0% by cycle 12.

Among the 21 resistant or intolerant CML patients who were in MMR at any time on treatment, the median time to first MMR was 2.76 months (95% CI: 0.03, 5.55). For the 17 newly diagnosed CML patients who achieved MMR, the median time to first MMR was 5.55 months (95% CI: 5.52, 5.75).

Among resistant or intolerant CML patients, the percentage of patients who achieved BCR-ABL/ABL ≤0.01% IS (MR4.0) by the cut-off date was 11.4%, while 4.5% of the patients achieved BCR-ABL/ABL ≤0.0032% IS (MR4.5). Among newly diagnosed patients, the percentage of patients who achieved MR4.0 was 32%, while 28.0% achieved MR4.5.

None of the 21 resistant or intolerant CML patients who were in MMR on treatment, had confirmed loss of MMR. Among the 17 newly diagnosed CML patients who achieved MMR, one patient had confirmed loss of MMR (the patient lost CHR due to an increase in basophil count, however, did not progress to AP/BC).

One resistant or intolerant CML patient progressed to AP/BC after about 10 months on treatment.

No deaths were reported on treatment or after treatment discontinuation in both studies.

### NON-CLINICAL SAFETY DATA

Nilotinib has been evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL), phototoxicity and carcinogenicity (rat and mice) studies.

#### Safety pharmacology and repeated dose toxicity

Nilotinib did not have effects on CNS or respiratory functions. *In vitro* cardiac safety studies demonstrated a preclinical signal for QT prolongation. No effects were seen in ECG measurements in dogs or monkeys treated up to 39 weeks or in a special telemetry study in dogs.

Repeated dose toxicity studies in dogs up to 4 weeks duration and in cynomolgus monkeys up to 9 months duration, revealed the liver as the primary target organ of toxicity of nilotinib. Alterations included increased alanine aminotransferase and alkaline phosphatase activity, and histopathology findings (mainly sinusoidal cell or Kupffer cell hyperplasia/hypertrophy, bile duct hyperplasia and periportal fibrosis). In general the changes in clinical chemistry were fully reversible after a four week recovery period, the histological alterations only showed partial reversibility. Exposures at the lowest dose levels where the liver effects were seen were lower than the exposure in humans at a dose of 800 mg/day. Only minor liver alterations were seen in mice or rats treated up to 26 weeks. Mainly reversible increases in cholesterol levels were seen in rats, dogs and monkeys.

#### Carcinogenicity and mutagenicity

Genotoxicity studies in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* systems with and without metabolic activation did not reveal any evidence for a mutagenic potential of nilotinib.

In the 2-year rat carcinogenicity study there was no evidence of carcinogenicity upon administration of nilotinib at 5, 15 and 40 mg/kg/day. Exposures (in terms of AUC) at the highest dose level were representing approximately 2 to 3 times human daily steady-state exposure (based on AUC) to nilotinib at the dose of 800mg/day. The major target organ for non-neoplastic lesions was the uterus (dilatation, vascular ectasia, hyperplasia endothelial cell, inflammation and/or epithelial hyperplasia).

In the 26-week Tg.rasH2 mouse carcinogenicity study, in which nilotinib was administered at 30, 100 and 300 mg/kg/day, skin papillomas/carcinomas were detected at 300 mg/kg, representing approximately 30 to 40 times (based on AUC) the human exposure at the maximum approved dose of 800 mg/day (administered as 400 mg twice daily). The No-Observed-Effect-Level for the skin neoplastic lesions was 100 mg/kg/day, representing approximately 10 to 20 times the human exposure at the maximum approved dose of 800 mg/day (administered as 400 mg twice daily). The major target organs for non-neoplastic lesions were the skin (epidermal hyperplasia), the growing teeth (degeneration/atrophy of the enamel organ of upper incisors and inflammation of the gingiva/odontogenic epithelium of incisors) and the thymus (increased incidence and/or severity of decreased lymphocytes).

In a juvenile development study, nilotinib was administered via oral gavage to juvenile rats from the first week postpartum through young adult (day 70 postpartum) at doses of 2, 6 and 20 mg/kg/day. Effects were limited to the dose of 20 mg/kg/day and consisted of reductions in body weight parameters and food consumption with recovery after dosing ceased. The No-Observed-Effect-level in juvenile rats was considered to be 6 mg/kg/day. Overall, the toxicity profile in juvenile rats was comparable to that observed in adult rats.

#### **Phototoxicity**

Nilotinib was shown to absorb light in the UV-B and UV-A range, and to be distributed into the skin showing a phototoxic potential *in vitro*. However, no phototoxicity has been observed *in vivo*. Therefore the risk that nilotinib causes photosensitization in patients is considered very low.

#### **INCOMPATIBILITIES**

Not applicable.

#### **STORAGE**

See folding box.

Tasigna should not be used after the date marked "EXPIRY" on the pack.

Tasigna must be kept out of the reach and sight of children.

#### **Manufacturer:**

See folding box.

A Product of Novartis Pharma AG, Basel, Switzerland

#### **Further information is available from**

Novartis Healthcare Pvt. Ltd.,  
Gala No. 1-A & 2-A, Bldg. No. 28, Arihant Compound,  
Kopar, Purna, Tal - Bhiwandi, Dist - Thane - 421 302, India.

Information issued: India package insert dtd 21 Aug 18 based on the IPL dtd 30 Jan 18.

® = Registered trademark of Novartis AG, Basle, Switzerland.

### **ANNEX – 3**

Copy of proposed Package Insert, label and carton

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.

## Mycophenolate Mofetil Tablets IP 250 mg / 500 mg

### **WARNING : EMBRYOFETAL TOXICITY, MALIGNANCIES AND SERIOUS INFECTIONS**

Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning.

Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe mycophenolate mofetil. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

### **Composition :**

Each film coated tablet contains :

Mycophenolate Mofetil IP 250 mg

Excipients q.s.

Colours : Black Oxide of Iron & Titanium Dioxide IP

### **Composition :**

Each film coated tablet contains :

Mycophenolate Mofetil IP 500 mg

Excipients q.s.

Colours : Red Oxide of Iron & Titanium Dioxide IP

### **DESCRIPTION**

Mycophenolate mofetil (MMF) is the 2-morpholinooethyl ester of mycophenolic acid (MPA), an inosine monophosphate dehydrogenase (IMPDH) inhibitor. Chemically MMF is 2-orphinoloyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobutyryl)-4-methyl-4-hexenoate. It has an empirical formula of  $C_{24}H_{36}NO_6$ , and a molecular weight of 433.50.

### **CLINICAL PHARMACOLOGY**

**Mechanism of action:** In the body, MMF is hydrolyzed to form MPA, which is the active metabolite. Mycophenolic acid is a potent, selective, uncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T and B-lymphocytes to both mitogenic and allo-specific stimulants. MPA also depresses synthesis of IgM by B lymphocytes. MPA prevents the glycosylation of lymphocyte membrane proteins that are involved in cellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. MMF does not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) or IL-2, but blocks the coupling of these events to DNA synthesis and proliferation.

**Pharmacokinetics:** MPA is rapidly and completely absorbed orally. Bioavailability of MPA is 94%. The mean ( $\pm SD$ ) apparent volume of distribution of MPA is approximately 4.0 ( $\pm 1.2$ ) L/kg following oral administration. Mean ( $\pm SD$ ) apparent half-life and plasma clearance of MPA are 17.9 ( $\pm 6.5$ ) hours and 193 ( $\pm 48$ ) mL/min following oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin.

MMF undergoes complete metabolism to MPA, the active metabolite. Metabolism to MPA occurs pre-systemically after oral dosing. MPA is metabolized principally by glucuronidation to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active. *In vivo*, MPAG is converted to MPA via enteropathic recirculation. Negligible amount of drug is excreted as MPA in the urine. Most of the orally administered dose is excreted in the urine as MPAG.

### **INDICATIONS**

The preparation shall be indicated for the prophylaxis of acute organ rejection and for the treatment of refractory organ rejection in patients receiving allogenic renal transplants increased graft, patients survival receiving allogenic cardiac transplants, and in patients receiving allogenic hepatic Transplantation use concomitantly with cyclosporine and corticosteroids.

### **DOSAGE AND ADMINISTRATION**

**Renal transplantation:** A dose of 1 g administered orally twice a day (daily dose of 2 g) is recommended for use in adult patients.

**Cardiac transplantation:** A dose of 1.5 g administered orally twice a day (daily dose of 3 g) is recommended for use in adult patients.

**Hepatic transplantation:** A dose 1.5 g administered orally twice a day (daily dose of 3 g) is recommended for use in adult patients.

Food has no effect on MPA AUC, but has been shown to decrease MPA  $C_{max}$  by 40%. It is recommended that MMF be administered on an empty stomach. However, in stable renal transplant patients, MMF may be administered with food if necessary.

### **CONTRAINDICATIONS**

MMF is contraindicated in patients with a hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product.

### **WARNINGS AND PRECAUTIONS**

**Lymphoma and malignancy:** Patients receiving immunosuppressive regimens involving combinations of drugs, including MMF, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

**Infections:** Over-suppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

**Latent viral infections:** Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include cases of progressive multifocal leukoencephalopathy (PML) and BK virus-associated nephropathy (BKVAN) which have been observed in patients receiving immunosuppressants, including MMF.

In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultations with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

BKVAN is associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

**Neutropenia:** Patients receiving MMF should be monitored for neutropenia. The development of neutropenia may be related to MMF itself, concomitant medications, viral infections, or combination of these causes. If neutropenia develops, dosing with MMF should be interrupted or the dose is reduced, appropriate diagnostic tests are performed, and the patient is managed appropriately. Patients receiving MMF should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

**Pure red cell aplasia:** Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MMF in combination with other immunosuppressive agents. The mechanism for MMF-induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of MMF therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

**Gastrointestinal disorder:** Gastrointestinal bleeding (requiring hospitalization) has been observed in patients treated with MMF. Gastrointestinal perforations have rarely been observed. Most patients receiving MMF were treated with MMF in combination with other immunosuppressive agents. Patients with active peptic ulcer disease were excluded from enrollment in studies with MMF. Because MMF has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, MMF should be administered with caution in patients with active severe digestive system disease.

**Patients with HGPRT deficiency:** On theoretical grounds, because MMF is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

**Immunizations:** During treatment with MMF, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective.

**Contraception:** Females of reproductive potential must use acceptable birth control during entire MMF therapy and for 6 weeks after stopping MMF, unless the patient chooses to avoid heterosexual intercourse completely (abstinence).

**Laboratory tests:** Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year.

### **ADVERSE REACTIONS**

The most common adverse reactions associated with the administration of MMF include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections. Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infection. Other adverse reactions reported in combination with cyclosporine and corticosteroids, are as follows:

**General:** Pain, abdominal pain, fever, headache, infection, sepsis, asthenia, chest pain, back pain, ascites, enlarged abdomen, abscess, accidental injury, cellulitis, chills with fever, facial edema, hemorrhage, hernia, laboratory test abnormality, malaise, neck pain, pelvic/pain peritonitis.

**Hematologic and lymphatic:** Anemia, leukopenia, thrombocytosis, hypochromic anemia, leukocytosis, coagulation disorder, ecchymosis, pancytopenia, petechia, polycythemia, prothrombin time increased, thromboplastin time increased.

**Cardiovascular:** Hypertension, hypotension, cardiac disorders, tachycardia, angina pectoris, atrial fibrillation, hypertension, palpitation, peripheral vascular disorder, postural hypotension, tachycardia, thrombosis, vasospasm, ventricular extrasystole, CHF, supraventricular tachycardia, ventricular tachycardia, atrial flutter, pulmonary hypertension, heart arrest, increased venous pressure, syncope, supraventricular extrasystole, pallor, vasospasm.

**Metabolic and nutritional:** Peripheral oedema, hypercholesterolemia, hypokalemia, hyperkalemia, hyperglycemia, increased creatinine, increased BUN, increased lactate dehydrogenase levels, hypomagnesemia, hypocalcemia.

**CNS:** Tremors, insomnia, dizziness, anxiety, depression, hypertension, paresthesia, somnolence, emotional lability, nonepileptic convulsions, hallucinations, abnormal thinking, vertigo.

**Dermatologic:** Alopecia, fungal dermatitis, hirsutism, pruritus, benign skin neoplasm, skin disorder, sweating, hemorrhage, skin carcinoma.

**Endocrine:** Diabetes, parathyroid disorder, Cushing's syndrome, and hypothyroidism.

**Gastrointestinal:** Diarrhea, constipation, nausea, dyspepsia, anorexia, esophagitis, flatulence, gastritis, gastroenteritis, GI hemorrhage, gingivitis, gum hyperplasia, hepatitis, ileus, infection, mouth ulceration; rectal disorder, liver damage, dysphagia, jaundice, stomatitis, thirst.

**Urogenital:** Urinary tract infection, kidney function abnormal, albuminuria, dysuria, hydronephrosis, impotence, pain, pyelonephritis, urinary frequency, nocturia, kidney failure, urine abnormality, hematuria, urinary incontinence, priapism, disorder, urinary retention.

**Musculoskeletal:** Arthritis, tendinitis, joint disorder, muscle cramps, myalgia, myasthenia.

**Respiratory:** Infection, dyspnea, cough increased, sinusitis, asthma, lung edema, pleural effusion, rhinitis, sinusitis, atelectasis, hiccup, pneumothorax, increased sputum, epistaxis, apnea, voice alteration, pain, hemoptysis, neoplasia, respiratory acidosis.

**Skin and appendages:** Rash.

**Special sense:** Amblyopia, cataract, conjunctivitis, ear pain, deafness, ear disorder, tinnitus, abnormal vision, lacrimation disorder, eye hemorrhage.

**Miscellaneous:** Abdominal enlargement, chills/fever, cyst, face edema, flu syndrome, hemorrhage, hermia, malaise, pelvic pain, ecchymosis, polycythemia, neck pain, cellulitis, increased prothrombin, decreased thromboplastin, periorbital edema, increased transaminases, weight loss, abnormal healing, dehydration.

**Lab test abnormalities:** Increased alkaline phosphatase, creatinine, gamma glutamyl transpeptidase, lactate dehydrogenase, AST and ALT, hypercalcemia, hyperlipidemia, hyperuricemia, hypervolemia, hypocalemia, hypoglycemia, hypoproteinemia, acidosis, hypoxia, hypophosphatemia, alkalis, hypocalcemia.

### **DRUG INTERACTIONS**

**Acyclovir:** Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate and acyclovir or its prodrug (eg, valacyclovir) to compete for tubular secretion, further increasing the concentrations of both drugs.

**Antacids:** With magnesium and aluminum hydroxides: MMF may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that MMF and the antacid not be administered simultaneously.

**Proton pump inhibitors:** Coadministration of PPIs (e.g., lansoprazole, pantoprazole) in single doses to healthy volunteers and multiple doses to transplant patients receiving has been reported to reduce the exposure to mycophenolic acid (MPA). The clinical impact of reduced MPA exposure on organ rejection has not been established in transplant patients receiving PPIs and MMF. Because clinical relevance has not been established, PPIs should be used with caution when coadministered to transplant patients being treated with MMF.

**Cholestyramine:** Cholestyramine has been found to reduce MPA AUC by approximately 40%. This decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG with cholestyramine in the intestine. Some degree of enterohepatic recirculation is also anticipated following intravenous administration of MMF. Therefore, MMF is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

**Cyclosporine:** In renal transplant patients, mean MPA exposure ( $AUC_{0-\infty}$ ) was approximately 30-50% greater when MMF is administered without cyclosporine compared with when MMF is coadministered with cyclosporine. This interaction is due to cyclosporine inhibition of multidrug-resistance-associated protein 2 (MRP-2) transporter in the biliary tract, thereby preventing the excretion of MPAG into the bile that would lead to enterohepatic recirculation of MPA. This information should be taken into consideration when MMF is used without cyclosporine.

**Gancyclovir:** No pharmacokinetic change has been observed between gancyclovir and MMF. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the two drugs will compete for tubular secretion and thus further increases in concentrations of both drugs may occur. In patients with renal impairment in which MMF and ganciclovir or its prodrug (eg, valganciclovir) are coadministered, the drugs should be monitored carefully.

**Oral contraceptives:** MMF may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. It is recommended to coadminister MMF with hormonal contraceptives (eg, birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution and additional barrier contraceptive methods must be used.

**Sevelamer:** Concomitant administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean  $AUC_{0-\infty}$  and  $AUC_{0-t}$ . This data suggest that sevelamer and other calcium free phosphate binders should not be administered simultaneously with MMF. Alternatively, it is recommended that sevelamer and other calcium free phosphate binders preferentially could be given 2 hours after MMF intake to minimize the impact on the absorption of MPA.

**Trimethoprim and sulfamethoxazole:** Trimethoprim 800 mg/ sulfamethoxazole 160 mg has not been found to affect bioavailability of MMF.

**Norfloxacin and metronidazole:** Following single dose administration of MMF, the mean MPA  $AUC_{0-\infty}$  was significantly reduced compared to the administration of mycophenolate mofetil alone. MMF is not recommended to be given with the combination of norfloxacin and metronidazole. There was no significant effect on mean MPA  $AUC_{0-\infty}$  when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately.

**Ciprofloxacin and amoxicillin plus clavulanic acid:** Approximately 50% reductions in median trough MPA concentrations (predose) from baseline (MMF alone) were observed in 3 days following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. These reductions in trough MPA concentrations tended to diminish within 14 days of antibiotic therapy and ceased within 3 days after discontinuation of antibiotics. The postulated mechanism for this interaction is an antibiotic-induced reduction in glucuronidase possessing enteric organisms leading to a decrease in enterohepatic recirculation of MPA. The change in trough level may not accurately represent changes in overall MPA exposure; therefore, clinical relevance of these observations is unclear.

**Rifampicin:** In a single heart-lung transplant patient, after correction for dose, a 67% decrease in MPA exposure ( $AUC_{0-\infty}$ ) has been observed with concomitant administration of mycophenolate mofetil and rifampin. Therefore, MMF is not recommended to be given with rifampin concomitantly unless the benefit outweighs the risk.

**Azathioprine:** It is recommended that MMF not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically.

**Other interactions:** The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, co-administration of probenecid, a known inhibitor of tubular secretion with mycophenolate mofetil results in a 3-fold increase in plasma MPAG AUC and a 2-fold increase in plasma MPA. These reductions in trough MPAG concentrations are likely to be due to increased tubular secretion of MPAG or the other drug undergoing tubular secretion. Drugs that alter the gastrointestinal flora may interact with mycophenolate mofetil by disrupting enteropathic recirculation. Interruption of MPAG hydrolysis may lead to less MPA available for absorption.

### **USE IN SPECIAL POPULATION**

**Pregnancy:** Pregnancy Category D. Use of MMF during pregnancy is associated with an increased risk of first trimester birth defects and risk of congenital malformations, especially edema and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. In animal studies, congenital malformations and pregnancy loss occurred when pregnant rats and rabbits received mycophenolic acid at dose multiples similar to and less than clinical doses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

**Nursing mothers:** Studies in rats treated with MMF have shown mycophenolic acid to be excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from MMF, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Geriatric use:** Clinical studies of MMF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between those elderly and younger patients. In general dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant or other drug therapy. Elderly patients may be at an increased risk of adverse reactions compared with younger individuals.

**Renal impairment:** Subjects with severe chronic renal impairment ( $GFR < 25 \text{ mL/min}/1.73 \text{ m}^2$ ) who have received single doses of MMF showed higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG. Doses of MMF greater than 1 g administered twice a day to renal transplant patients should be avoided as they should be carefully observed.

In patients with delayed renal graft function posttransplant, mean MPA  $AUC_{0-\infty}$  was comparable, but MPAG  $AUC_{0-\infty}$  was 2-fold to 3-fold higher, compared to that seen in posttransplant patients without delayed renal graft function. No dose adjustment is recommended for these patients; however, they should be carefully observed.

**Patients with hepatic impairment:** No dose adjustments are recommended for renal patients with severe hepatic parenchymal disease. However, it is not known whether dose adjustments are needed for hepatic disease with other etiologies.

### **OVERDOSE:**

There has been no reported experience of overdose of MMF in humans. The highest dose administered to renal transplant patients in clinical trials was 4 g/day. In acute toxicity studies, no deaths occurred at doses up to 1000 mg/kg/day in animals. At doses up to 1000 mg/kg/day there were no signs of toxicity in dogs. These doses represent 11 times the recommended clinical dose in renal transplant patients. MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations ( $> 100 \mu\text{g/mL}$ ), small amounts of MPAG are removed. By increased excretion of the drug, MPAG can be removed by beta acid sequestrants, such as cholestyramine.

**Storage :** Store protected from light & moisture, at a temperature not exceeding 30°C.

**Presentation:** A blister strip of 10 tablets.

**Manufactured by :**

**Emcure**

**PHARMACEUTICALS LTD.**

Lane No. 3, Phase - II, SIDCO,

Bari - Brahmana, Jammu - 181 133, India.

SAPCODE

**Front**

**Back**

Product	Mycophenolate Mofetil Tablets IP 250 mg/500 mg	New / Revised A/W	New Artwork	FDA Lic. Availability	Avail.
<b>Dosage form</b>	Tablets	<b>Reason for change</b>	N.A.	<b>Proof 1</b>	21.03.2019
<b>Therapeutic Category</b>	Immunosuppressant	<b>Colour Scheme</b>	Black	<b>Corrections of Proof 1</b>	
<b>Item</b>	Pack insert A/W	<b>Pantone Shades</b>	N.A.	<b>Proof 2</b>	
<b>Dimension</b>	L. 80 x 250 mm (Folded 80 x 31.5 mm)	<b>Total No. of Colours</b>	1	<b>Corrections of Proof 2</b>	
<b>Substrate</b>	Super white maplitho paper	<b>Special Effect (if any)</b>	N.A.	<b>Proof 3</b>	
<b>Specification</b>	60 GSM	<b>Item Code</b>	SAPCODE	<b>Corrections of Proof 3</b>	
<b>Printing Area</b>	F/F	<b>Marketing Division</b>		<b>Final</b>	
<b>Item Style</b>	N.A.	<b>Design / Colour Approved on</b>	N.A.	<b>A/W Checked by</b>	PMD Cell
<b>A/W Proportion</b>	Same Size	<b>Vendor</b>		<b>A/W Verified by</b>	Production / QC
<b>Product Status</b>	Emcure Own Jammu Unit	<b>Country</b>	Domestic	<b>A/W Approved by</b>	Unit Head
<b>Remark (If any) :</b>	New Artwork				

*For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.*

Rx

# Mycophenolate Mofetil Tablets IP 250 mg / 500 mg

## **WARNING : EMBRYOFETAL TOXICITY, MALIGNANCIES AND SERIOUS INFECTIONS**

Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning.

Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma. Only physicians experienced in immunosuppressive therapy and management of renal, cardiac or hepatic transplant patients should prescribe mycophenolate mofetil. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

### **Composition :**

Each film coated tablet contains :

Mycophenolate Mofetil IP 250 mg

Excipients q.s.

Colours : Black Oxide of Iron & Titanium Dioxide IP

### **Composition :**

Each film coated tablet contains :

Mycophenolate Mofetil IP 500 mg

Excipients q.s.

Colours : Red Oxide of Iron & Titanium Dioxide IP

### **DESCRIPTION**

Mycophenolate mofetil (MMF) is the 2-morpholinoethyl ester of mycophenolic acid (MPA), an inosine monophosphate dehydrogenase (IMPDH) inhibitor. Chemically MMF is 2-orpholinoethyl (E)-6-(1,3-dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoate. It has an empirical formula of  $C_{23}H_{31}NO_7$ , and a molecular weight of 433.50.

### **CLINICAL PHARMACOLOGY**

**Mechanism of action:** In the body, MMF is hydrolyzed to form MPA, which is the active metabolite. Mycophenolic acid is a potent, selective, uncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), and therefore inhibits the *de novo* pathway of guanosine nucleotide synthesis without incorporation into DNA. Because T and B-lymphocytes are critically dependent for their proliferation on *de novo* synthesis of purines, whereas other cell types can utilize salvage pathways, MPA has potent cytostatic effects on lymphocytes. MPA inhibits proliferative responses of T- and B-lymphocytes to both mitogenic and allospecific stimulation. MPA also suppresses antibody formation by B lymphocytes. MPA prevents the glycosylation of lymphocyte and monocyte glycoproteins that are involved in intercellular adhesion to endothelial cells and may inhibit recruitment of leukocytes into sites of inflammation and graft rejection. MMF does not inhibit early events in the activation of human peripheral blood mononuclear cells, such as the production of interleukin-1 (IL-1) and interleukin-2 (IL-2), but blocks the coupling of these events to DNA synthesis and proliferation.

**Pharmacokinetics:** MPA is rapidly and completely absorbed orally. Bioavailability of MPA is 94%. The mean ( $\pm SD$ ) apparent volume of distribution of MPA is approximately 4.0 ( $\pm 1.2$ ) L/kg following oral administration. Mean ( $\pm SD$ ) apparent half-life and plasma clearance of MPA are 17.9 ( $\pm 6.5$ ) hours and 193 ( $\pm 48$ ) mL/min following oral administration, respectively. MPA, at clinically relevant concentrations, is 97% bound to plasma albumin.

MMF undergoes complete metabolism to MPA, the active metabolite. Metabolism to MPA occurs pre-systemically after oral dosing. MPA is metabolized principally by glucuronyl transferase to form the phenolic glucuronide of MPA (MPAG), which is not pharmacologically active. *In vivo*, MPAG is converted to MPA via enterohepatic recirculation. Negligible amount of drug is excreted as MPA in the urine. Most of the orally administered dose is excreted in the urine as MPAG.

## **INDICATIONS**

The preparation shall be indicated for the prophylaxis of acute organ rejection and for the treatment of refractory organ rejection in patients receiving allogenic renal transplants increased graft, patients survival receiving allogenic cardiac transplants, and in patients receiving allogenic hepatic Transplantation use concomitantly with cyclosporin and corticosteroids.

## **DOSAGE AND ADMINISTRATION**

**Renal transplantation:** A dose of 1 g administered orally twice a day (daily dose of 2 g) is recommended for use in adult patients.

**Cardiac transplantation:** A dose of 1.5 g administered orally twice a day (daily dose of 3 g) is recommended for use in adult patients.

**Hepatic transplantation:** A dose 1.5 g administered orally twice a day (daily dose of 3 g) is recommended for use in adult patients.

Food has no effect on MPA AUC, but has been shown to decrease MPA  $C_{max}$  by 40%. It is recommended that MMF be administered on an empty stomach. However, in stable renal transplant patients, MMF may be administered with food if necessary.

## **CONTRAINdications**

MMF is contraindicated in patients with a hypersensitivity to mycophenolate mofetil, mycophenolic acid or any component of the drug product.

## **WARNINGS AND PRECAUTIONS**

**Lymphoma and malignancy:** Patients receiving immunosuppressive regimens involving combinations of drugs, including MMF, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.

**Infections:** Over-suppression of the immune system can also increase susceptibility to infection, including opportunistic infections, fatal infections, and sepsis.

**Latent viral infections:** Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include cases of progressive multifocal leukoencephalopathy (PML) and BK virus-associated nephropathy (BKVAN) which have been observed in patients receiving immunosuppressants, including MMF.

In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms and consultation with a neurologist should be considered as clinically indicated. Consideration should be given to reducing the amount of immunosuppression in patients who develop PML. In transplant patients, physicians should also consider the risk that reduced immunosuppression represents to the graft.

BKVAN is associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

**Neutropenia:** Patients receiving MMF should be monitored for neutropenia. The development of neutropenia may be related to MMF itself, concomitant medications, viral infections, or combination of these causes. If neutropenia develops, dosing with MMF should be interrupted or the dose is reduced, appropriate diagnostic tests are performed, and the patient is managed appropriately. Patients receiving MMF should be instructed to report immediately any evidence of infection, unexpected bruising, bleeding or any other manifestation of bone marrow depression.

**Pure red cell aplasia:** Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MMF in combination with other immunosuppressive agents. The mechanism for MMF-induced PRCA is unknown; the relative contribution of other immunosuppressants and their combinations in an immunosuppression regimen are also unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of MMF therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk.

**Gastrointestinal disorder:** Gastrointestinal bleeding (requiring hospitalization) has been observed in patients treated with MMF. Gastrointestinal perforations have rarely been observed. Most patients receiving MMF were also receiving other drugs known to be associated with these complications. Patients with active peptic ulcer disease were excluded from enrollment in studies with MMF. Because MMF has been associated with an increased incidence of digestive system adverse events, including infrequent cases of gastrointestinal tract ulceration, hemorrhage, and perforation, MMF should be administered with caution in patients with active serious digestive system disease.

**Patients with HGPRT deficiency:** On theoretical grounds, because MMF is an IMPDH (inosine monophosphate dehydrogenase) inhibitor, it should be avoided in patients with rare hereditary deficiency of hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

**Immunizations:** During treatment with MMF, the use of live attenuated vaccines should be avoided and patients should be advised that vaccinations may be less effective.

**Contraception:** Females of reproductive potential must use acceptable birth control during entire MMF therapy and for 6 weeks after stopping MMF, unless the patient chooses to avoid heterosexual intercourse completely (abstinence).

**Laboratory tests:** Complete blood counts should be performed weekly during the first month, twice monthly for the second and third months of treatment, then monthly through the first year.

#### **ADVERSE EFFECTS**

The principal adverse reactions associated with the administration of MMF include diarrhea, leukopenia, sepsis, vomiting, and there is evidence of a higher frequency of certain types of infections. Serious life-threatening infections such as meningitis and infectious endocarditis have been reported occasionally and there is evidence of a higher frequency of certain types of serious infections such as tuberculosis and atypical mycobacterial infection. Other adverse reactions reported in combination with cyclosporine and corticosteroids, are as follows:

**General:** Pain, abdominal pain, fever, headache, infection, sepsis, asthenia, chest pain, back pain, ascites, enlarged abdomen, abscess, accidental injury, cellulitis, chills with fever, facial oedema, hemorrhage, hernia, laboratory test abnormality, malaise, neck pain, pelvic pain, peritonitis.

**Hematologic and lymphatic:** Anemia, leukopenia, thrombocytosis, hypochromic anemia, leukocytosis, coagulation disorder, ecchymosis, pancytopenia, petechia, polycythemia, prothrombin time increased, thromboplastin time increased.

**Cardiovascular:** Hypertension, hypotension, cardiac disorders, tachycardia, angina pectoris, atrial fibrillation, hypotension, palpitation, peripheral vascular disorder, postural hypotension, tachycardia, thrombosis, vasodilation, ventricular extrasystole, CHF, supraventricular tachycardia, ventricular tachycardia, atrial flutter, pulmonary hypertension, heart arrest, increased venous pressure, syncope, supraventricular extrasystole, pallor, vasospasm.

**Metabolic and nutritional:** Peripheral oedema, hypercholesterolemia, hypokalemia, hyperkalemia, hyperglycemia, increased creatinine, increased BUN, increased lactate dehydrogenase levels, hypomagnesemia, hypocalcemia.

**CNS:** Tremors, insomnia, dizziness, anxiety, depression, hypertonia, paresthesia, somnolence, emotional lability, neuropathy, convulsion, hallucinations, abnormal thinking, vertigo.

**Dermatologic:** Alopecia, fungal dermatitis, hirsutism, pruritus, benign skin neoplasm, skin disorder, sweating, hemorrhage, skin carcinoma.

**Endocrine:** Diabetes, parathyroid disorder, Cushing's syndrome, and hypothyroidism.

**Gastrointestinal:** Diarrhoea, constipation, nausea, dyspepsia, anorexia, esophagitis, flatulence, gastritis, gastroenteritis, GI hemorrhage, gingivitis, gum hyperplasia, hepatitis, ileus, infection, mouth ulceration; rectal disorder, liver damage, dysphagia, jaundice, stomatitis, thirst.

**Urogenital:** Urinary tract infection, kidney function abnormal, albuminuria, dysuria, hydronephrosis, impotence, pain, pyelonephritis, urinary frequency, nocturia, kidney failure, urine abnormality, hematuria, urinary incontinence, prostatic disorder, urinary retention.

**Musculoskeletal:** Arthralgia, joint disorder, leg cramps myalgia, myasthenia.

**Respiratory:** Infection, dyspnoea, cough increased, sinusitis, asthma, lung edema, pleural effusion, rhinitis, sinusitis, atelectasis, hiccup, pneumothorax, increased sputum, epistaxis, apnea, voice alteration, pain, hemoptysis, neoplasm, respiratory acidosis.

**Skin and appendages:** Rash.

**Special sense:** Amblyopia, cataract, conjunctivitis, ear pain, deafness, ear disorder, tinnitus, abnormal vision, lacrimation disorder, eye hemorrhage.

**Miscellaneous:** Abdomen enlarged, chills/fever, cyst, face edema, flu syndrome, hemorrhage, hernia, malaise, pelvic pain, ecchymosis, polycythemia, neck pain, cellulitis, increased prothrombin, decreased thromboplastin, petechia, phlebitis, thrombosis, weight gain/loss, abnormal healing dehydration.

**Lab test abnormalities:** Increased alkaline phosphatase, creatinine, gamma glutamyl transpeptidase, lactic dehydrogenase, AST and ALT, hypercalcemia, hyperlipemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hypoproteinemia, acidosis, hypoxia, hypophosphatemia, alkalosis, hypochloremia.

## DRUG INTERACTIONS

**Acyclovir:** Because MPAG plasma concentrations are increased in the presence of renal impairment, as are acyclovir concentrations, the potential exists for mycophenolate and acyclovir or its prodrug (eg, valacyclovir) to compete for tubular secretion, further increasing the concentrations of both drugs.

**Antacids with magnesium and aluminum hydroxides:** MMF may be administered to patients who are also taking antacids containing magnesium and aluminum hydroxides; however, it is recommended that MMF and the antacid not be administered simultaneously.

**Proton pump inhibitors:** Coadministration of PPIs (e.g., lansoprazole, pantoprazole) in single doses to healthy volunteers and multiple doses to transplant patients receiving has been reported to reduce the exposure to mycophenolic acid (MPA). The clinical impact of reduced MPA exposure on organ rejection has not been established in transplant patients receiving PPIs and MMF. Because clinical relevance has not been established, PPIs should be used with caution when coadministered to transplant patients being treated with MMF.

**Cholestyramine:** Cholestyramine has been found to reduce MPA AUC by approximately 40%. This decrease is consistent with interruption of enterohepatic recirculation which may be due to binding of recirculating MPAG with cholestyramine in the intestine. Some degree of enterohepatic recirculation is also anticipated following intravenous administration of MMF. Therefore, MMF is not recommended to be given with cholestyramine or other agents that may interfere with enterohepatic recirculation.

**Cyclosporine:** In renal transplant patients, mean MPA exposure ( $AUC_{0-12h}$ ) was approximately 30-50% greater when MMF is administered without cyclosporine compared with when MMF is coadministered with cyclosporine. This interaction is due to cyclosporine inhibition of multidrug-resistance-associated protein 2 (MRP-2) transporter in the biliary tract, thereby preventing the excretion of MPAG into the bile that would lead to enterohepatic recirculation of MPA. This information should be taken into consideration when MMF is used without cyclosporine.

**Gancyclovir:** No pharmacokinetic interaction has been observed between gancyclovir and MMF. Because MPAG plasma concentrations are increased in the presence of renal impairment, as are ganciclovir concentrations, the two drugs will compete for tubular secretion and thus further increases in concentrations of both drugs may occur. In patients with renal impairment in which MMF and ganciclovir or its prodrug (eg, valganciclovir) are coadministered, patients should be monitored carefully.

**Oral contraceptives:** MMF may not have any influence on the ovulation-suppressing action of the studied oral contraceptives. It is recommended to coadminister MMF with hormonal contraceptives (eg, birth control pill, transdermal patch, vaginal ring, injection, and implant) with caution and additional barrier contraceptive methods must be used.

**Sevelamer:** Concomitant administration of sevelamer and mycophenolate mofetil in adult and pediatric patients decreased the mean MPA  $C_{max}$  and  $AUC_{0-12h}$ . This data suggest that sevelamer and other calcium free phosphate binders should not be administered simultaneously with MMF. Alternatively, it is recommended that sevelamer and other calcium free phosphate binders preferentially could be given 2 hours after MMF intake to minimize the impact on the absorption of MPA.

**Trimethoprim and sulfamethoxazole:** Trimethoprim 800 mg/ sulfamethoxazole 160 mg has not been found to affect bioavailability of MMF.

**Norfloxacin and metronidazole:** Following single dose administration of MMF, the mean MPA  $AUC_{0-48h}$  was significantly reduced compared to the administration of mycophenolate mofetil alone. MMF is not recommended to be given with the combination of norfloxacin and metronidazole. There was no significant effect on mean MPA  $AUC_{0-48h}$  when mycophenolate mofetil was concomitantly administered with norfloxacin or metronidazole separately.

**Ciprofloxacin and amoxicillin plus clavulanic acid:** Approximately 50% reductions in median trough MPA concentrations (predose) from baseline (MMF alone) were observed in 3 days following commencement of oral ciprofloxacin or amoxicillin plus clavulanic acid. These reductions in trough MPA concentrations tended to diminish within 14 days of antibiotic therapy and ceased within 3 days after discontinuation of antibiotics. The postulated mechanism for this interaction is an antibiotic-induced reduction in glucuronidase-possessing enteric organisms leading to a decrease in enterohepatic recirculation of MPA. The change in trough level may not accurately represent changes in overall MPA exposure; therefore, clinical relevance of these observations is unclear.

**Rifampicin:** In a single heart-lung transplant patient, after correction for dose, a 67% decrease in MPA exposure ( $AUC_{0-12h}$ ) has been observed with concomitant administration of mycophenolate mofetil and rifampin. Therefore, MMF is not recommended to be given with rifampin concomitantly unless the benefit outweighs the risk.

**Azathioprine:** It is recommended that MMF not be administered concomitantly with azathioprine because both have the potential to cause bone marrow suppression and such concomitant administration has not been studied clinically.

**Other interactions:** The measured value for renal clearance of MPAG indicates removal occurs by renal tubular secretion as well as glomerular filtration. Consistent with this, co-administration of probenecid, a known inhibitor of tubular secretion, with mycophenolate mofetil results in a 3-fold increase in plasma MPAG AUC and a 2-fold increase in plasma MPA AUC. Thus, other drugs known to undergo renal tubular secretion may compete with MPAG and thereby raise plasma concentrations of MPAG or the other drug undergoing tubular secretion. Drugs that alter the gastrointestinal flora may interact with mycophenolate mofetil by disrupting enterohepatic recirculation. Interference of MPAG hydrolysis may lead to less MPA available for absorption.

## **USE IN SPECIAL POPULATION**

**Pregnancy:** Pregnancy Category D. Use of MMF during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations, especially external ear and other facial abnormalities including cleft lip and palate, and anomalies of the distal limbs, heart, esophagus, and kidney. In animal studies, congenital malformations and pregnancy loss occurred when pregnant rats and rabbits received mycophenolic acid at dose multiples similar to and less than clinical doses. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

**Nursing mothers:** Studies in rats treated with MMF have shown mycophenolic acid to be excreted in milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from MMF, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Geriatric use:** Clinical studies of MMF did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal or cardiac function and of concomitant or other drug therapy. Elderly patients may be at an increased risk of adverse reactions compared with younger individuals.

**Renal impairment:** Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73 m<sup>2</sup>) who have received single doses of MMF showed higher plasma MPA and MPAG AUCs relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG. Doses of MMF greater than 1 g administered twice a day to renal transplant patients should be avoided and they should be carefully observed.

In patients with delayed renal graft function posttransplant, mean MPA AUC<sub>(0-12h)</sub> was comparable, but MPAG AUC<sub>(0-12h)</sub> was 2-fold to 3-fold higher, compared to that seen in posttransplant patients without delayed renal graft function. No dose adjustment is recommended for these patients; however, they should be carefully observed.

**Patients with hepatic impairment:** No dose adjustments are recommended for renal patients with severe hepatic parenchymal disease. However, it is not known whether dose adjustments are needed for hepatic disease with other etiologies.

## **OVERDOSAGE:**

There has been no reported experience of overdose of MMF in humans. The highest dose administered to renal transplant patients in clinical trials has been 4 g/day. In acute oral toxicity studies, no deaths occurred in adult mice at doses up to 4000 mg/kg or in adult monkeys at doses up to 1000 mg/kg; these were the highest doses of MMF tested in these species. These doses represent 11 times the recommended clinical dose in renal transplant patients. MPA and MPAG are usually not removed by hemodialysis. However, at high MPAG plasma concentrations (>100 µg/mL), small amounts of MPAG are removed. By increasing excretion of the drug, MPA can be removed by bile acid sequestrants, such as cholestyramine.

**Storage :** Store protected from light & moisture, at a temperature not exceeding 30°C.

**Presentation :** A blister strip of 10 tablets.

Manufactured by :

**Emcure**

**PHARMACEUTICALS LTD.**

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SAPCODE