**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

Tabrecta 150 mg film-coated tablets
Tabrecta 200 mg film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tabrecta 150 mg film-coated tablets

Each film-coated tablet contains capmatinib dihydrochloride monohydrate equivalent to 150 mg capmatinib.

Tabrecta 200 mg film-coated tablets

Each film-coated tablet contains capmatinib dihydrochloride monohydrate equivalent to 200 mg capmatinib.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet (tablet)

Tabrecta 150 mg film-coated tablets

Pale orange brown, ovaloid, curved film-coated tablet with bevelled edges, unscored, debossed with "DU" on one side and "NVR" on the other side. Approximate size: 18.3 mm (length) x 7.3 mm (width).

Tabrecta 200 mg film-coated tablets

Yellow, ovaloid, curved film-coated tablet with bevelled edges, unscored, debossed with "LO" on one side and "NVR" on the other side. Approximate size: 20.3 mm (length) x 8.1 mm (width).

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Tabrecta as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) harbouring alterations leading to mesenchymal-epithelial transition factor gene exon 14 (METex14) skipping, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy.

## 4.2 Posology and method of administration

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

Patients have to be selected for treatment with Tabrecta based on the presence of genetic alterations leading to a METex14 skipping mutation in tumour tissue or plasma specimens using a validated test. If a genetic alteration is not detected in a plasma specimen, tumour tissue should be tested (see sections 4.4 and 5.1).

Posology

The recommended dose of Tabrecta is 400 mg orally twice daily with or without food.

Treatment should be continued based on individual safety and tolerability and as long as the patient is deriving clinical benefit from therapy.

If a dose of Tabrecta is missed or vomiting occurs, the patient should not make up for the dose, but take the next dose at the scheduled time.

*Dose modifications*
The recommended dose reduction schedule for the management of adverse reactions based on individual safety and tolerability is listed in Table 1.

**Table 1 Tabrecta dose reduction schedule**

| **Dose level** | **Dose and schedule** | **Number and strength of tablets** |
|---|---|---|
| Starting dose | 400 mg twice daily | Two 200 mg tablets / twice daily |
| First dose reduction | 300 mg twice daily | Two 150 mg tablets / twice daily |
| Second dose reduction | 200 mg twice daily | One 200 mg tablet / twice daily |

Doses of Tabrecta below 200 mg twice daily have not been investigated in clinical studies.

Recommendations for dose modifications of Tabrecta for adverse reactions are provided in Table 2.

**Table 2 Tabrecta dose modifications for the management of adverse reactions**

| **Adverse reaction** | **Severity** | **Dose modification** |
|---|---|---|
| Interstitial lung disease (ILD)/pneumonitis | Any grade treatment-related | Permanently discontinue Tabrecta. |
| Isolated ALT and/or AST elevations from baseline, without concurrent total bilirubin increase | Grade 3 (>5.0 to ≤20.0 x ULN) | Temporarily withhold Tabrecta until recovery to baseline ALT/AST grade.<br>If recovered to baseline within 7 days, then resume Tabrecta at the same dose, otherwise resume Tabrecta at a reduced dose as per Table 1. |
| | Grade 4 (>20.0 x ULN) | Permanently discontinue Tabrecta. |
| Combined elevations in ALT and/or AST with concurrent total bilirubin increase, in the absence of cholestasis or haemolysis | If patient develops ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN, irrespective of baseline grade | Permanently discontinue Tabrecta. |

| | | |
|---|---|---|
| Isolated total bilirubin elevation from baseline, without concurrent ALT and/or AST increase | Grade 2 (>1.5 to ≤3.0 x ULN) | Temporarily withhold Tabrecta until recovery to baseline bilirubin grade.<br>If recovered to baseline within 7 days, then resume Tabrecta at the same dose, otherwise resume Tabrecta at a reduced dose as per Table 1. |
| | Grade 3 (>3.0 to ≤10.0 x ULN) | Temporarily withhold Tabrecta until recovery to baseline bilirubin grade.<br>If recovered to baseline within 7 days, then resume Tabrecta at a reduced dose as per Table 1, otherwise permanently discontinue Tabrecta. |
| | Grade 4 (>10.0 x ULN) | Permanently discontinue Tabrecta. |
| Serum creatinine increased | Grade 2 (>1.5 to ≤3.0 x ULN) | Temporarily withhold Tabrecta until recovery to baseline serum creatinine grade.<br>If recovered to baseline, then resume Tabrecta at the same dose level. |
| | Grade 3 (>3.0 to ≤6.0 x ULN) | Temporarily withhold Tabrecta until recovery to baseline serum creatinine grade.<br>If recovered to baseline, then resume Tabrecta at a reduced dose as per Table 1. |
| | Grade 4 (>6.0 x ULN) | Permanently discontinue Tabrecta. |
| Vomiting | Grade 2 | Temporarily withhold Tabrecta until resolved to grade ≤1.<br>If resolved to grade ≤1 then resume Tabrecta the same dose level. |
| | Grade 3 | Temporarily withhold Tabrecta until resolved to grade ≤2.<br>If resolved to grade ≤2 then resume Tabrecta at a reduced dose as per Table 1. |
| | Grade 4 | Temporarily withhold Tabrecta until resolved to grade ≤2.<br>If resolved to grade ≤2 then resume Tabrecta at a reduced dose as per Table 1. |

| | | |
|---|---|---|
| Other adverse reactions | Grade 2 | Maintain dose level. If intolerable, consider temporarily withholding Tabrecta until resolved, then resume Tabrecta at a reduced dose as per Table 1. |
| | Grade 3 | Temporarily withhold Tabrecta until resolved, then resume Tabrecta at a reduced dose as per Table 1. |
| | Grade 4 | Permanently discontinue Tabrecta. |
| Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.<br>Grading according to CTCAE Version 4.03 (CTCAE = Common Terminology Criteria for Adverse Events).<br>Baseline = at the time of treatment initiation. | | |

*Special populations*
*Elderly*
No dose adjustment is necessary in patients 65 years of age or older (see section 5.2).

*Renal impairment*
Caution should be exercised in patients with severe renal impairment as Tabrecta has not been studied in these patients. No dose adjustment is necessary in patients with mild or moderate renal impairment (see section 5.2).

*Hepatic impairment*
No dose adjustment is necessary in patients with mild, moderate or severe hepatic impairment (see section 5.2).

*Paediatric population*
The safety and efficacy of Tabrecta in children aged 0 to 18 years have not been established. No data are available.

Method of administration

Tabrecta should be taken orally twice daily with or without food. Patients with swallowing difficulties are recommended to take Tabrecta with food. The tablets should be swallowed whole to ensure that the full dose is administered.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for use

Assessment of METex14 skipping alterations status

When detecting the presence of alterations leading to METex14 skipping using tissue-based or plasma-based specimens, it is important that a well-validated and robust test is chosen to avoid false negative or false positive results. For the characteristics of tests used in clinical studies see section 5.1.

Interstitial lung disease (ILD)/pneumonitis

ILD/pneumonitis, which can be fatal, has occurred in patients treated with Tabrecta (see section 4.8). Prompt investigation should be performed in any patient with new or worsening of pulmonary symptoms indicative of ILD/pneumonitis (e.g. dyspnoea, cough, fever). Tabrecta should be immediately withheld in patients with suspected ILD/pneumonitis and permanently discontinued if no other potential causes of ILD/pneumonitis are identified (see section 4.2).

Hepatic effects

Transaminase elevations have occurred in patients treated with Tabrecta (see section 4.8). Liver function tests (including ALT, AST and total bilirubin) should be performed prior to the start of treatment, every 2 weeks during the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients who develop transaminase or bilirubin elevations. Based on the severity of the adverse reaction, temporarily withhold, dose reduce, or permanently discontinue Tabrecta (see section 4.2).

Elevations of pancreatic enzymes

Elevations in amylase and lipase levels have occurred in patients treated with Tabrecta (see section 4.8). Amylase and lipase should be monitored at baseline and regularly during treatment with Tabrecta. Based on the severity of the adverse reaction, temporarily withhold, dose reduce, or permanently discontinue Tabrecta (see section 4.2).

Embryo-foetal toxicity

Based on findings from animal studies and its mechanism of action, Tabrecta can cause foetal harm when administered to a pregnant woman due to its foetotoxicity and teratogenicity (see section 4.6). Pregnant women and women of childbearing potential should be advised of the potential risk to a foetus if Tabrecta is used during pregnancy or if the patient becomes pregnant while taking Tabrecta. Sexually active women of childbearing potential should use effective contraception during treatment with Tabrecta and for at least 7 days after the last dose. The pregnancy status of women of childbearing potential should be verified prior to starting treatment with Tabrecta.

Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during treatment with Tabrecta and for at least 7 days after the last dose.

Risk of photosensitivity

Based on findings from animal studies, there is a potential risk of photosensitivity reactions with Tabrecta (see section 5.3). In Study GEOMETRY mono-1, it was recommended that patients limit direct ultraviolet exposure during treatment with Tabrecta and adopt the following protective measures: use of sunscreen on exposed parts of the body, wearing of protective clothing and sunglasses. These measures should be continued for at least 7 days after the last dose.

Interaction with other medicinal products

There is a potential for drug-drug interactions with Tabrecta as victim or perpetrator (see section 4.5).

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

## 4.5 Interaction with other medicinal products and other forms of interaction

Capmatinib undergoes metabolism through CYP3A4 enzyme and aldehyde oxidase. The risk of a drug-drug interaction via aldehyde oxidase has not been evaluated as there are no confirmed clinically relevant inhibitors.

Effect of other medicinal products on Tabrecta

*Strong CYP3A inhibitors*
In healthy subjects, co-administration of a single 200 mg capmatinib dose with the strong CYP3A inhibitor itraconazole (200 mg once daily for 10 days) increased capmatinib $AUC_{inf}$ by 42% with no change in capmatinib $C_{max}$ compared to administration of capmatinib alone. Patients should be closely monitored for adverse reactions during co-administration of Tabrecta with strong CYP3A inhibitors, including but not limited to, clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole.

*Strong CYP3A inducers*
In healthy subjects, co-administration of a single 400 mg capmatinib dose with the strong CYP3A inducer rifampicin (600 mg once daily for 9 days) decreased capmatinib $AUC_{inf}$ by 67% and decreased $C_{max}$ by 56% compared to administration of capmatinib alone. Decreases in capmatinib exposure may decrease Tabrecta anti-tumour activity. Co-administration of Tabrecta with strong CYP3A inducers, including but not limited to, carbamazepine, phenobarbital, phenytoin, rifampicin and St. John's wort *(Hypericum perforatum)*, should be avoided. An alternative medicinal product with no or minimal potential to induce CYP3A should be considered.

*Moderate CYP3A inducers*
Simulations using physiologically-based pharmacokinetic (PBPK) models predicted that co-administration of a 400 mg capmatinib dose with the moderate CYP3A inducer efavirenz (600 mg daily for 20 days) would result in a 44% decrease in capmatinib $AUC_{0-12h}$ and 34% decrease in $C_{max}$ at steady-state compared to administration of capmatinib alone. Decreases in capmatinib exposure may decrease Tabrecta anti-tumour activity. Caution should be exercised during co-administration of Tabrecta with moderate CYP3A inducers.

*Agents that raise gastric pH*
Capmatinib demonstrates pH-dependent solubility and becomes poorly soluble as pH increases *in vitro*. In healthy subjects, co-administration of a single 600 mg capmatinib dose with the proton pump inhibitor rabeprazole (20 mg once daily for 4 days) decreased capmatinib $AUC_{inf}$ by 25% and decreased $C_{max}$ by 38% compared to administration of capmatinib alone. Clinically relevant drug-drug interactions between capmatinib and gastric-acid-reducing agents are unlikely to occur as co-administration of rabeprazole had no clinically meaningful effect on exposure of capmatinib.

Effect of Tabrecta on other medicinal products

*Substrates of CYP enyzmes*
Moderate inhibition of CYP1A2 was observed when capmatinib was co-administered with the sensitive CYP1A2 substrate caffeine. Co-administration of capmatinib (400 mg twice daily) with caffeine increased caffeine $AUC_{inf}$ by 134%. If capmatinib is co-administered with narrow therapeutic index CYP1A2 substrates, such as theophylline and tizanidine, dose reduction of the co-administered medicinal product may be required.

Clinically relevant drug-drug interactions between capmatinib and CYP3A substrates are unlikely to occur as co-administration of capmatinib had no clinically meaningful effect on exposure of midazolam (a CYP3A substrate).

*P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrates*
In cancer patients, co-administration of digoxin (P-gp substrate) with multiple doses of capmatinib (400 mg twice daily) increased digoxin $AUC_{inf}$ by 47% and increased $C_{max}$ by 74% compared to administration of digoxin alone. In cancer patients, co-administration of rosuvastatin (BCRP substrate) with multiple doses of capmatinib (400 mg twice daily) increased rosuvastatin $AUC_{inf}$ by 108% and increased $C_{max}$ by 204% compared to administration of rosuvastatin alone. Co-administration of Tabrecta with a P-gp or BCRP substrate may increase the incidence and severity of adverse reactions of these substrates. Caution should be exercised during co-administration of Tabrecta with P-gp (digoxin, dabigatran etexilate, colchicine, sitagliptin, saxagliptin and posaconazole) or BCRP (methotrexate, rosuvastatin, pravastatin, mitoxantrone and sulphasalazine) substrates. If capmatinib is co-administered with narrow therapeutic index P-gp or BCRP substrates, dose reduction of the co-administered medicinal product may be required.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Sexually-active women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with Tabrecta and for at least 7 days after the last dose.

Male patients with sexual partners who are pregnant, possibly pregnant, or who could become pregnant should use condoms during treatment with Tabrecta and for at least 7 days after the last dose.

Pregnancy

There are no data from the use of capmatinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Based on findings from animal studies and its mechanism of action, capmatinib is suspected to cause congenital malformations when administered during pregnancy. Tabrecta should not be used during pregnancy unless the clinical condition of the woman requires treatment with capmatinib.

The pregnancy status of women of childbearing potential should be verified prior to starting treatment with Tabrecta.

Breast-feeding

It is unknown whether capmatinib or its metabolites are excreted in human milk after administration of Tabrecta. There is insufficient information on the excretion of capmatinib or its metabolites in animal milk. A risk to the breast-fed infant cannot be excluded. Because of the potential for serious adverse reactions in breast-fed infants, breast-feeding should be discontinued during treatment with Tabrecta and for at least 7 days after the last dose.

Fertility

No human fertility data on capmatinib are available. Fertility studies with capmatinib were not conducted in animals.

## 4.7 Effects on ability to drive and use machines

Tabrecta has no or negligible influence on the ability to drive and use machines.

## 4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are peripheral oedema (67.5%), nausea (44.4%), fatigue (34.4%), blood creatinine increased (33.8%), vomiting (25.0%), dyspnoea (22.5%), decreased appetite (21.3%) and back pain (20.6%). The most common grade 3 or 4 adverse reactions are peripheral oedema (14.4%), lipase increased (9.4%), ALT increased (8.1%), fatigue (8.1%), dyspnoea (6.9%) and amylase increased (5.6%).

Serious adverse reactions were reported in 35 of 160 patients (21.9%) who received Tabrecta. Serious adverse reactions in >2% of patients included dyspnoea (5.6%), ILD/pneumonitis (5.0%), cellulitis (3.1%) and peripheral oedema (2.5%).

Dose interruptions were reported in 81 of 160 patients (50.6%). Adverse reactions requiring dose interruption included peripheral oedema (15.0%), blood creatinine increased (11.3%), lipase increased (8.1%), nausea (8.1%), ALT increased (6.3%), fatigue (5.6%), amylase increased (5.0%), vomiting (5.0%), dyspnoea (3.8%), blood bilirubin increased (3.1%) and AST increased (3.1%).

Dose reductions were reported in 49 of 160 patients (30.6%). Adverse reactions requiring dose reductions included peripheral oedema (16.3%), ALT increased (5.0%), blood creatinine increased (3.8%), fatigue (3.1%) and nausea (2.5%).

Permanent discontinuation was reported in 19 of 160 patients (11.9%). The most frequent adverse reactions leading to permanent discontinuation of Tabrecta were ILD/pneumonitis (3.8%), peripheral oedema (2.5%), ALT increased (1.3%), AST increased (1.3%), blood bilirubin increased (1.3%), blood creatinine increased (1.3%), lipase increased (1.3%), amylase increased (0.6%), fatigue (0.6%) and urticaria (0.6%).

Tabulated list of adverse reactions

The safety of Tabrecta was evaluated in patients with locally-advanced or metastatic NSCLC in a pivotal, global, prospective, multi-cohort, non-randomised, open-label Phase II study (GEOMETRY mono-1) across all cohorts (N=373), regardless of prior treatment or MET dysregulation (mutation and/or amplification) status. The frequencies of adverse reactions are based on all-cause adverse event frequencies identified in 160 patients with METex14 skipping mutations exposed to capmatinib at the recommended dose, whereas frequencies for changes in laboratory parameters are based on worsening from baseline shifts by at least 1 grade (grading according to CTCAE version 4.03). The safety profile for all GEOMETRY mono-1 patients (N=373) and for patients with METex14 skipping mutations (N=160) is comparable. The median duration of exposure to capmatinib across MET-mutated cohorts was 34.9 weeks (range: 0.4 to 195.7 weeks). Among patients who received capmatinib, 55.0% were exposed for at least 6 months and 36.3% were exposed for at least one year.

Adverse reactions from clinical studies (Table 3) are listed by MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse reaction is based on the following convention: 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

**Table 3 Adverse reactions in patients (N=160) harbouring METex14 skipping mutations in study GEOMETRY mono-1 (Data cut-off: 30-Aug-2021)**

| Adverse reaction | All grades Frequency category | All grades % | Grade 3/4 % |
|---|---|---|---|
| **Infections and infestations** | | | |
| Cellulitis | Common | 4.4 | 2.5* |
| **Metabolism and nutrition disorders** | | | |
| Decreased appetite | Very common | 21.3 | 1.3* |
| **Respiratory, thoracic, and mediastinal disorders** | | | |
| Dyspnoea | Very common | 22.5 | 6.9* |
| Cough | Very common | 17.5 | 0.6* |
| ILD/pneumonitis[1] | Common | 7.5 | 4.4* |
| **Gastrointestinal disorders** | | | |
| Vomiting | Very common | 25.0 | 0.6* |
| Nausea | Very common | 44.4 | 0.6* |
| Diarrhoea | Very common | 15.6 | - |
| Constipation | Very common | 13.1 | 1.3* |
| **Skin and subcutaneous tissue disorders** | | | |
| Pruritus | Very common | 10.6 | 0.6* |
| Rash[2] | Common | 9.4 | - |
| Urticaria | Common | 2.5 | 0.6* |
| **General disorders and administration site conditions** | | | |
| Oedema peripheral[3] | Very common | 67.5 | 14.4* |
| Pyrexia | Very common | 10.6 | 1.3* |
| Fatigue[4] | Very common | 34.4 | 8.1* |
| Back pain | Very common | 20.6 | 1.3* |
| Weight decreased | Very common | 12.5 | - |
| Non-cardiac chest pain[5] | Common | 9.4 | 1.3* |
| **Investigations** | | | |
| Albumin decreased | Very common | 78.3 | 1.9* |
| Creatinine increased | Very common | 74.5 | 0.6* |
| Alanine aminotransferase increased | Very common | 45.9 | 11.5 |
| Amylase increased | Very common | 37.2 | 7.1 |
| Lipase increased | Very common | 33.3 | 11.5 |
| Aspartate aminotransferase increased | Very common | 33.8 | 5.7 |
| Phosphate decreased | Very common | 30.1 | 4.5 |
| Sodium decreased | Very common | 22.3 | 4.5 |
| Bilirubin increased | Common | 8.3 | 0.6* |

1 ILD/pneumonitis includes preferred terms (PTs) of ILD, pneumonitis and organising pneumonia.
2 Rash includes PTs of rash, rash maculopapular and rash vesicular.
3 Oedema peripheral includes PTs of oedema peripheral and peripheral swelling.
4 Fatigue includes PTs of fatigue and asthenia.
5 Non-cardiac chest pain includes PTs of chest discomfort, musculoskeletal chest pain and non-cardiac chest pain.
* No grade 4 adverse reactions reported in GEOMETRY mono-1 patients with METex14 skipping mutations.

Cases of acute kidney injury (n=1), renal failure (n=4) and acute pancreatitis (n=1) were reported in GEOMETRY mono-1 MET-amplified patients.

Description of selected adverse reactions

*ILD/pneumonitis*
Any grade ILD/pneumonitis was reported in 12 of 160 patients (7.5%). Grade 3 ILD/pneumonitis was reported in 7 patients (4.4%), with one fatal event of treatment-related pneumonitis (0.6%) and one fatal event of organising pneumonia (0.6%). ILD/pneumonitis occurred in 6 of 63 patients (9.5%) with a history of prior radiotherapy and 6 of 97 patients (6.2%) who did not receive prior radiotherapy. Six patients (3.8%) discontinued Tabrecta due to ILD/pneumonitis. ILD/pneumonitis mostly occurred within approximately the first 3 months of treatment. The median time-to-onset of grade 3 or higher ILD/pneumonitis was 7.0 weeks (range: 0.7 to 88.4 weeks).

*Hepatic effects*
Any grade ALT/AST elevations were reported in 24 of 160 patients (15.0%). Grade 3 or 4 ALT/AST elevations were observed in 13 of 160 patients (8.1%) treated with Tabrecta. Two patients (1.3%) discontinued Tabrecta due to ALT/AST elevations. ALT/AST elevations mostly occurred within approximately the first 3 months of treatment. The median time-to-onset of grade 3 or higher ALT/AST elevations was 6.4 weeks (range: 2.1 to 17.9 weeks).

*Elevations of pancreatic enzymes*
Any grade amylase/lipase elevations were reported in 27 of 160 patients (16.9%). Grade 3 or 4 amylase/lipase elevations were reported in 18 of 160 patients (11.3%) treated with Tabrecta. Three patients (1.9%) discontinued Tabrecta due to amylase/lipase elevations. The median time to onset of grade 3 or higher amylase/lipase elevations was 10.1 weeks (range: 2.3 to 68.0 weeks).

*Peripheral oedema*
Any grade peripheral oedema was reported in 108 of 160 patients (67.5%). This adverse reaction includes the PTs of peripheral oedema, which was the most frequent at 65.0% and peripheral swelling which occurred in 4.4% of patients. Grade 3 or 4 peripheral oedema was reported in 23 of 160 patients (14.4%) treated with Tabrecta. Four patients (2.5%) discontinued Tabrecta due to peripheral oedema. The median time to onset of grade 3 or higher peripheral oedema was 24.3 weeks (range: 1.4 to 86.9 weeks).

Special populations

*Elderly*
Of the 160 patients with METex14 skipping mutations in the GEOMETRY mono-1 study who received 400 mg capmatinib twice daily, 85% were 65 years or older, and 4.4% were 85 years or older. The occurrence of grade ≥3 events increased with age. Treatment-related serious events were more frequent in patients aged ≥65 to <75 years (22%) and those aged ≥85 years (28.6%) when compared to those patients aged ≥75 to <85 years (8.5%) and patients younger than 65 years (8.3%), although this comparison is limited by the small sample size in patients aged ≥85 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

## 4.9 Overdose

There is limited experience with overdose in clinical studies with Tabrecta. Patients should be closely monitored for signs or symptoms of adverse reactions, and general supportive measures and symptomatic treatment should be initiated in cases of suspected overdose.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX17.

Mechanism of action

Capmatinib is an inhibitor of the MET receptor tyrosine kinase. Capmatinib inhibits MET phosphorylation (both autophosphorylation and phosphorylation triggered by the ligand hepatocyte growth factor [HGF]), MET-mediated phosphorylation of downstream signalling proteins, as well as proliferation and survival of MET-dependent cancer cells.

Pharmacodynamic effects

*Cardiac electrophysiology*
Capmatinib did not prolong the QT interval to any clinically relevant extent following administration of Tabrecta at the recommended dose.

*Detection of METex14 skipping status*
In GEOMETRY mono-1, MET exon 14 skipping mutations were determined using a qualitative real-time PCR test (RT-PCR) designed to detect exon 14-deleted MET mRNA derived from formalin-fixed, paraffin-embedded human tissue. The test is indicated as an aid in selecting non-small cell lung cancer (NSCLC) patients whose tumours carry a MET mutation that causes in-frame deletion of the entire exon 14 (141 bases) in mRNA for treatment with capmatinib.

Clinical efficacy and safety

The efficacy of capmatinib for the treatment of patients with locally advanced or metastatic NSCLC with a MET exon 14 (METex14) skipping mutation was studied in a prospective, multi-cohort, non-randomised, open-label Phase II Study GEOMETRY mono-1. Patients (N=373) were enrolled into study cohorts based on their prior treatment and MET dysregulation (mutation and/or amplification) status. Patients with a METex14 skipping mutation (N=160) were enrolled into the MET-mutated cohorts regardless of MET amplification. The demonstrated efficacy of capmatinib is based on Cohorts 4 and 6 which enrolled 100 previously-treated patients.

In the MET-mutated cohorts, eligible NSCLC patients were required to have Epidermal Growth Factor Receptor (EGFR) wild-type (for exon 19 deletions and exon 21 L858R substitution mutations) and Anaplastic Lymphoma Kinase (ALK) negative status, and a METex14 skipping mutation with at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, along with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 1. Patients with symptomatic central nervous system (CNS) metastases who were neurologically unstable or required increasing doses of steroids within the prior 2 weeks to manage CNS symptoms, patients with clinically significant uncontrolled cardiac disease, or patients pre-treated with any MET or HGF inhibitor were not eligible for the study.

In the MET-mutated cohorts, a total of 100 adult previously-treated patients with locally advanced or metastatic NSCLC with a METex14 skipping mutation were enrolled and treated with Tabrecta. The patients had been treated with 1 or 2 prior lines of systemic therapy for advanced disease, except for 3 patients (3.0%) who had received 3 prior lines before receiving capmatinib. The median duration of exposure to capmatinib was 27.9 weeks.

Patients continued treatment until documented disease progression, intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit.

The demographic characteristics of the previously-treated patients were 56% female, median age 70 years (range: 49 to 90 years), 29% aged 75 years of age or older, 73% white, 24% Asian, 1.0% black, 59% never smoked, 37% were former smokers, 78% had adenocarcinoma, 26% had ECOG PS 0, 73% had ECOG PS 1, and 17% had CNS metastases. The majority of patients (62%) had stage IV disease. Ninety-one percent of patients had prior chemotherapy, 86% had prior platinum-based chemotherapy, 32% had prior immunotherapy, and 16% had received 2 prior systemic therapies.

The primary endpoint of the study was overall response rate (ORR) as determined by a Blinded Independent Review Committee (BIRC) according to RECIST 1.1. The key secondary endpoint was duration of response (DOR) by BIRC.

Efficacy results from Study GEOMETRY mono-1 for previously-treated NSCLC patients with a METex14 skipping mutation are summarised in Table 4.

**Table 4 Efficacy results by BIRC in previously-treated NSCLC patients with a METex14 skipping mutation who received Tabrecta in GEOMETRY mono-1 (data cut-off: 30-Aug-2021)**

| **Efficacy parameters** | **Overall previously treated population (N=100)** | **Cohort 4 (2/3L) N=69** | **Cohort 6 (2L) N=31** |
|---|---|---|---|
| **Overall response rate[a] (95% CI)[b]** | 44.0% (34.1, 54.3) | 40.6% (28.9, 53.1) | 51.6% (33.1, 69.8) |
| Complete response (CR), n (%) | 1 (1.0) | 1 (1.4) | 0 (0.0) |
| Partial response (PR), n (%) | 43 (43.0) | 27 (39.1) | 16 (51.6) |
| **Duration of response[a]** | | | |
| Number of responders, n | 44 | 28 | 16 |
| Median, months (95% CI)[c] | 9.72 (5.62, 12.98) | 9.72 (5.55, 12.98) | 9.05 (4.17, NE) |

Abbreviations: CI, confidence interval; NE, not estimable.
ORR: CR+PR.
[a] Determined by RECIST v1.1.
[b] Clopper and Pearson exact binomial 95% CI.
[c] Based on Kaplan-Meier estimate.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Tabrecta in all subsets of the paediatric population in the treatment of lung malignant neoplasm (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Capmatinib exhibited dose-proportional increases in systemic exposure ($AUC_{inf}$ and $C_{max}$) across the dose range tested (200 to 400 mg twice daily). Steady-state is expected to be achieved after approximately 3 days after oral dosing of capmatinib 400 mg twice daily, with a geometric mean accumulation ratio of 1.39 (coefficient of variation (CV): 42.9%). Inter-individual variability of $C_{max}$ and $AUC_{tau}$ was estimated to be 38% and 40%, respectively.

Absorption

In humans, absorption is rapid after oral administration of capmatinib. Under fasted conditions, peak plasma levels of capmatinib ($C_{max}$) were reached approximately 1 to 2 hours ($T_{max}$) after an oral 400 mg dose of capmatinib tablets in cancer patients. Under fed conditions, $T_{max}$ is approximately 4-6 hours. The absorption of capmatinib tablets after oral administration is estimated to be greater than 70%.

*Food effect*
Food does not alter capmatinib bioavailability to a clinically meaningful extent. Tabrecta can be administered with or without food (see section 4.2).

When capmatinib was administered with food in healthy subjects, oral administration of a single 600 mg dose with a high-fat meal increased capmatinib $AUC_{inf}$ by 46% and no change in $C_{max}$ compared to when capmatinib was administered under fasted conditions. A low-fat meal in healthy subjects had no clinically meaningful effect on capmatinib exposure.

When capmatinib was administered at 400 mg twice daily in cancer patients, exposure ($AUC_{0-12h}$) was similar after administration of capmatinib with food and under fasted conditions.

Distribution

Capmatinib is 96% bound to human plasma proteins, independent of concentration. The apparent mean volume of distribution at steady-state (Vss/F) is 164 litres in cancer patients.

The blood-to-plasma ratio was 1.5 (concentration range of 10 to 1000 ng/ml), but decreased at higher concentrations to 0.9 (concentration 10000 ng/ml), indicating a saturation of distribution into red blood cells.

Capmatinib crosses the blood-brain barrier (see section 5.3).

Biotransformation

*In vitro* and *in vivo* studies indicated that capmatinib is cleared mainly through metabolism driven by cytochrome P450 (CYP) 3A4 (40-50%) and aldehyde oxidase (40%). The biotransformation of capmatinib occurs essentially by Phase I metabolic reactions including C-hydroxylation, lactam formation, N-oxidation, N-dealkylation, carboxylic acid formation, and combinations thereof. Phase II reactions involve glucuronidation of oxygenated metabolites. The most abundant radioactive component in plasma is unchanged capmatinib (42.9% of radioactivity $AUC_{0-12h}$). The major circulating metabolite, M16 (CMN288), is pharmacologically inactive and accounts for 21.5% of the radioactivity in plasma $AUC_{0-12h}$.

Elimination

The effective elimination half-life (calculated based on geometric mean accumulation ratio) of capmatinib is 6.54 hours. The geometric mean steady-state apparent oral clearance (CLss/F) of capmatinib was 19.8 litres/hour.

Capmatinib is eliminated mainly through metabolism, and subsequent faecal excretion. Following a single oral administration of [14C]-capmatinib capsule to healthy subjects, 78% of the total radioactivity was recovered in the faeces and 22% in the urine. Excretion of unchanged capmatinib in urine is negligible.

Special populations

*Elderly*
No overall differences in the safety or effectiveness were observed between patients aged 65 and 75 years or older and younger patients.

*Effect of age, gender, race and body weight*
Population pharmacokinetic analysis showed that there is no clinically relevant effect of age, gender, race, or body weight on the systemic exposure of capmatinib.

*Renal impairment*
Based on a population pharmacokinetic analysis that included 207 patients with normal renal function (creatinine clearance [CLcr] ≥90 ml/min), 200 patients with mild renal impairment (CLcr 60 to 89 ml/min), and 94 patients with moderate renal impairment (CLcr 30 to 59 ml/min), mild or moderate renal impairment had no clinically significant effect on the exposure of capmatinib. Tabrecta has not been studied in patients with severe renal impairment (CLcr 15 to 29 ml/min) (see section 4.2).

*Hepatic impairment*
A study was conducted in non-cancer subjects with various degrees of hepatic impairment based on Child-Pugh classification using a 200 mg single-dose of capmatinib. The geometric mean systemic exposure ($AUC_{inf}$) of capmatinib was decreased by approximately 23% and 9% in subjects with mild (N=6) and moderate (N=8) hepatic impairment, respectively, and increased by approximately 24% in subjects with severe (N=6) hepatic impairment compared to subjects with normal (N=9) hepatic function. Mild, moderate or severe hepatic impairment had no clinically significant effect on the exposure of capmatinib.

Pharmacokinetic/pharmacodynamic relationship

Capmatinib exposure-response relationships and the time course of the pharmacodynamic response are unknown.

*In vitro* evaluation of medicinal product interaction potential

*Interactions between enzymes and Tabrecta*
*In vitro* studies showed that capmatinib is an inhibitor of CYP2C8, CYP2C9 and CYP2C19. Capmatinib also showed weak induction of CYP2B6 and CYP2C9 in cultured human hepatocytes. Simulations using PBPK models predicted that capmatinib given at a dose of 400 mg twice daily is unlikely to cause clinically relevant interaction via CYP2B6, CYP2C8, CYP2C9 or CYP2C19.

*Interactions between transporters and Tabrecta*
Based on *in vitro* data, capmatinib is a P-gp substrate, but not a BCRP or multidrug resistance-associated (MRP2) substrate. Capmatinib is not a substrate of transporters involved in active hepatic uptake in primary human hepatocytes.

Based on *in vitro* data, capmatinib and its major metabolite CMN288 showed reversible inhibition of renal transporters MATE1 and MATE2K. Capmatinib may inhibit MATE1 and MATE2K at clinically relevant concentrations.

Based on *in vitro* data, capmatinib showed reversible inhibition of hepatic uptake transporters OATP1B1, OATP1B3, and OCT1. However, capmatinib is not expected to cause clinically relevant inhibition of OATP1B1, OATP1B3, and OCT1 uptake transporters based on the concentration achieved at the therapeutic dose. Capmatinib is not an inhibitor of renal transporters OAT1 or OAT3. Capmatinib is not a MRP2 inhibitor *in vitro*.

## 5.3 Preclinical safety data

Repeated-dose toxicity

Signs indicative of CNS toxicity (such as tremors and/or convulsions), and histopathological findings of white matter vacuolation in the thalamus/caudate/putamen regions of the midbrain were observed in rats at doses ≥2.9 exposure multiples of the human clinical exposure based on AUC at the 400 mg twice daily dose. No signs of CNS toxicity or brain abnormalities were observed in cynomolgus monkey studies. The relevance of the CNS findings in rats to humans is unknown.

Capmatinib crossed the blood-brain barrier in rats with a brain-to-blood exposure ($AUC_{inf}$) ratio of approximately 9%.

A reversible, minimal-to-mild subcapsular neutrophilic infiltration associated with single cell necrosis was seen in the liver of male monkeys treated for 13 weeks at dose levels of ≥4.7 exposure multiples of the human clinical exposure based on AUC at the 400 mg twice daily dose.

Genotoxicity

Capmatinib is not genotoxic based on a standard battery of *in vitro* and *in vivo* tests.

Reproductive toxicity

In embryo-foetal development studies in rats and rabbits, capmatinib was teratogenic and foetotoxic at dose levels not eliciting maternal toxicity. In rats, decreased foetal weight and increased incidence of litters and foetuses with limb malformations were observed at the maternal exposure of ≥0.89 exposure multiples of the anticipated clinical exposure (based on the AUC). In rabbits, limb, lung and tongue malformations were seen at the maternal exposure of ≥0.025 exposure multiples of the anticipated clinical exposure.

Photosensitivity

*In vitro* and *in vivo* photosensitisation assays with capmatinib suggested that capmatinib has the potential for photosensitisation.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Tablet core

Cellulose microcrystalline
Mannitol
Crospovidone
Povidone
Magnesium stearate
Silica colloidal anhydrous
Sodium laurilsulfate

Film-coating

*Tabrecta 150 mg film-coated tablets*
Hypromellose
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide, yellow (E172)
Iron oxide, red (E172)
Iron oxide, black (E172)

*Tabrecta 200 mg film-coated tablets*
Hypromellose
Titanium dioxide (E171)
Macrogol
Talc
Iron oxide, yellow (E172)

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

3 years.

### 6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

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

### 6.5 Nature and contents of container

PCTFE/PVC (polychlorotrifluoroethylene/polyvinyl chloride) blisters backed with an aluminium lidding foil.

Packs containing 60 or 120 film-coated tablets.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1650/001-004

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

Lek Pharmaceuticals d.d.
Trimlini 2D
9220 Lendava
Slovenia

Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF UNIT PACK**

## 1. NAME OF THE MEDICINAL PRODUCT

Tabrecta 150 mg film-coated tablets
capmatinib

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains capmatinib dihydrochloride monohydrate equivalent to 150 mg capmatinib.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

60 film-coated tablets
120 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

| | |
|---|---|
| EU/1/22/1650/001 | 60 tablets |
| EU/1/22/1650/002 | 120 tablets |

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Tabrecta 150 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Tabrecta 150 mg tablets
capmatinib

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON OF UNIT PACK**

## 1. NAME OF THE MEDICINAL PRODUCT

Tabrecta 200 mg film-coated tablets
capmatinib

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains capmatinib dihydrochloride monohydrate equivalent to 200 mg capmatinib.

## 3. LIST OF EXCIPIENTS

## 4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

60 film-coated tablets
120 film-coated tablets

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

## 9. SPECIAL STORAGE CONDITIONS

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

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

## 12. MARKETING AUTHORISATION NUMBER(S)

| | |
|---|---|
| EU/1/22/1650/003 | 60 tablets |
| EU/1/22/1650/004 | 120 tablets |

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Tabrecta 200 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

## 1. NAME OF THE MEDICINAL PRODUCT

Tabrecta 200 mg tablets
capmatinib

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the patient**

**Tabrecta 150 mg film-coated tablets**
**Tabrecta 200 mg film-coated tablets**
capmatinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What Tabrecta is and what it is used for

**What Tabrecta is**
Tabrecta contains the active substance capmatinib, which belongs to a class of medicines called protein kinase inhibitors.

**What Tabrecta is used for**
Tabrecta is a medicine used to treat adults with a type of lung cancer called non-small cell lung cancer (NSCLC). It is used if the lung cancer is advanced or has spread to other parts of the body (metastatic) and is caused by a change (mutation) in a gene that makes an enzyme called MET.

Your tumour or blood will be tested for certain mutations in this gene. Your cancer is likely to respond to treatment with Tabrecta if the test result is positive.

**How Tabrecta works**
Tabrecta helps to slow down or stop the growth and spread of your lung cancer if it is caused by a mutation in a gene that makes MET.

If you have any questions about how Tabrecta works or why this medicine has been prescribed for you, ask your doctor or pharmacist.

## 2. What you need to know before you take Tabrecta

**Do not take Tabrecta**
- if you are allergic to capmatinib or any of the other ingredients of this medicine (listed in section 6).

**Warnings and precautions**
Talk to your doctor, pharmacist or nurse before taking Tabrecta:
- if you have or have had lung or breathing problems other than your lung cancer.
- if you have or have had liver problems.
- if you have or have had pancreatic problems.

Limit direct exposure to the sun or artificial ultraviolet (UV) light while using Tabrecta. Use sunscreen, wear sunglasess and clothes that cover your skin, and avoid sunbathing while you are taking Tabrecta and for at least 7 days after you stop taking it.

**Monitoring during your treatment with Tabrecta**
Your doctor will do blood tests before you start treatment with Tabrecta to check your liver and pancreatic function. Your doctor will continue to check your liver and pancreatic function during treatment with Tabrecta.

**Children and adolescents**
Do not give this medicine to children and adolescents below 18 years of age because it has not yet been studied in this age group.

**Other medicines and Tabrecta**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines

It is particularly important that you mention any of the following medicines:
- medicines used to treat seizures, such as carbamazepine, phenobarbital, phenytoin
- St. John's wort (also known as *Hypericum perforatum*), a herbal product used to treat depression and other conditions
- medicines used to treat tuberculosis, such as rifampicin
- antibiotics used to treat bacterial infections, such as telithromycin, clarithromycin
- medicines used to treat fungal infections, such as ketoconazole, itraconazole, posaconazole, voriconazole
- medicines used to treat HIV/AIDS, such as ritonavir (either alone or in combination with lopinavir), saquinavir, indinavir, nelfinavir, efavirenz
- medicines used to treat hepatitis, such as telaprevir
- medicines used to treat depression, such as nefazodone
- medicines used to treat high blood pressure or heart problems, such as verapamil
- medicines used to treat breathing problems, such as theophylline
- medicines used to treat muscle spasms, such as tizanidine
- medicines used to treat heart problems, such as digoxin
- medicines used to treat blood clots, such as dabigatran etexilate
- medicines used to treat gout, such as colchicine
- medicines used to treat diabetes, such as sitagliptin, saxagliptin
- medicines used to treat high cholesterol, such as rosuvastatin, pravastatin
- medicines used to treat certain types of cancer or autoimune diseases, such as methotrexate, mitoxantrone
- sulfasalazine, a medicine used to treat bowel and rheumatic joint inflammation

Ask your doctor, pharmacist or nurse if you are not sure whether you are taking any of the medicines listed above.

You should also tell your doctor if you are prescribed a new medicine when you are already taking Tabrecta.

**Pregnancy and breast-feeding**
Tabrecta can harm your unborn baby. If you are a woman who could become pregnant, your doctor will perform a pregnancy test before starting treatment with Tabrecta in order to ensure that you are not pregnant. You should use an effective method of contraception while taking Tabrecta and for at least 7 days after you stop taking it to avoid becoming pregnant. Ask your doctor about effective methods of contraception.

If you do become pregnant, or think you may be pregnant, while taking Tabrecta, tell your doctor straight away. Your doctor will discuss with you the potential risks of taking Tabrecta during pregnancy.

If you are a man with a partner who is pregnant or who could become pregnant you should use a condom while taking Tabrecta and for at least 7 days after you stop taking it.

It is not known if Tabrecta passes into breast milk. You should not breast-feed while you are taking Tabrecta and for at least 7 days after you stop taking it.

**Driving and using machines**
Tabrecta is not expected to affect your ability to drive or use machines.

**Tabrecta contains sodium**
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

## 3. How to take Tabrecta

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Do not exceed the recommended dose prescribed by your doctor.

**How much Tabrecta to take**
The recommended dose is 400 mg (two 200 mg tablets) taken by mouth twice a day with or without food. Taking Tabrecta twice a day at about the same time each day will help you to remember when to take your medicine. If you have difficulties swallowing tablets, take Tabrecta tablets with food.

Your doctor will tell you exactly how many tablets of Tabrecta to take. Your doctor may change the dose during treatment with Tabrecta if you have certain side effects. Do not change the dose without talking to your doctor.

Swallow Tabrecta tablets whole. Do not break, chew or crush the tablets.

If you vomit after you have taken Tabrecta, do not take any more Tabrecta tablets until it is time for your next dose.

**How long to take Tabrecta**
Continue taking Tabrecta for as long as your doctor tells you.

This is a long-term treatment, possibly lasting for months or years. Your doctor will monitor your condition to check that the treatment is having the desired effect.

If you have questions about how long to take Tabrecta, talk to your doctor or pharmacist.

**If you take more Tabrecta than you should**
If you have taken too much Tabrecta, or if someone else accidentally takes your medicine, contact a doctor or hospital for advice immediately. Show the pack of Tabrecta. Medical treatment may be necessary.

**If you forget to take Tabrecta**
Do not take a double dose to make up for a forgotten dose. Instead, wait until it is time for your next dose.

**If you stop taking Tabrecta**
Your doctor may temporarily or permanently stop treatment with Tabrecta if you have certain side effects. Do not stop taking your medicine unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Some side effects could be serious**
If you get any of the serious side effects listed below, **tell your doctor immediately.** They may advise you to stop taking the medicine or may change your dose.

**Very common:** may affect more than 1 in 10 people
- Abnormal blood test results such as a high level of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) which may be a sign of liver problems
- Abnormal blood test results such as a high level of amylase and/or lipase which may be a sign of pancreatic problems

**Common:** may affect up to 1 in every 10 people
- Abnormal blood test results such as a high level of bilirubin which may be a sign of liver problems
- Cough, fever, trouble breathing, shortness of breath, or wheezing which may be a sign of inflammation of the lungs (pneumonitis, interstitial lung disease)
- Passing urine less often than usual or passing smaller amounts of urine than usual which may be a sign of kidney problems (renal failure, acute kidney injury)

**Uncommon:** may affect up to 1 in every 100 people
- Severe upper stomach pain which may be a sign of inflammation of the pancreas (acute pancreatitis)

**Other possible side effects**
Other side effects include the following listed below. If these side effects become severe, tell your doctor, pharmacist or nurse.

**Very common:** may affect more than 1 in 10 people
- Swollen hands, ankles or feet (peripheral oedema)
- Nausea and/or vomitting
- Tiredeness and/or weakness (fatigue, asthenia)
- Shortness of breath (dyspnoea)
- Loss of appetite
- Changes in bowel movements (diarrhoea or constipation)
- Back pain
- Cough
- Pain in your chest
- Fever (pyrexia)
- Decreased weight

**Common:** may affect up to 1 in every 10 people
- Itching with or without a rash (pruritus or urticaria)
- Skin rash
- Pain, tenderness, redness, warmth, or swelling of your skin which may be a sign of bacterial skin infection (cellulitis)

**Abnormal blood test results**
During Tabrecta treatment, the results of blood tests may be abnormal which may be a sign of problems with your kidney, liver, or electrolytes. These include the following:

**Very common:** may affect more than 1 in 10 people
- Low level of albumin in the blood
- High level of creatinine in the blood (a substance excreted by the kidney)
- Low level of phosphate in the blood
- Low level of sodium in the blood

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Tabrecta

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and the blister foil after EXP. The expiry date refers to the last day of that month.
- This medicine does not require any special temperature storage conditions. Store in the original package in order to protect from moisture.
- Do not use this medicine if you notice any damage to the packaging or if there are any signs of tampering.
- Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

**What Tabrecta contains**
- The active substance is capmatinib.
- Each 150 mg film-coated tablet contains capmatinib dihydrochloride monohydrate equivalent to 150 mg capmatinib.
- Each 200 mg film-coated tablet contains capmatinib dihydrochloride monohydrate equivalent to 200 mg capmatinib.
- The other ingredients are:
    - Tablet core: cellulose microcrystalline; mannitol; crospovidone; povidone; magnesium stearate; silica colloidal anhydrous; sodium laurilsulfate (see “Tabrecta contains sodium” in section 2).
    - Film coating (150 mg): Hypromellose; titanium dioxide (E171); macrogol; talc; iron oxide, yellow (E172); iron oxide, red (E172); iron oxide, black (E172).
    - Film coating (200 mg): Hypromellose; titanium dioxide (E171); macrogol; talc; iron oxide, yellow (E172).

**What Tabrecta looks like and contents of the pack**

Tabrecta 150 mg film-coated tablets (tablets) are pale orange brown ovaloid tablets. They have “DU” on one side and “NVR” on the other side. Approximate size: 18.3 mm (length) x 7.3 mm (width).

Tabrecta 200 mg film-coated tablets (tablets) are yellow ovaloid tablets. They have “LO” on one side and “NVR” on the other side. Approximate size: 20.3 mm (length) x 8.1 mm (width).

Tabrecta film-coated tablets are provided in blisters and are available in packs containing 60 or 120 film-coated tablets.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
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Elm Park, Merrion Road
Dublin 4
Ireland

**Manufacturer**
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Roonstrasse 25
90429 Nuremberg
Germany

Lek Pharmaceuticals d.d.
Trimlini 2D
9220 Lendava
Slovenia

Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
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**Other sources of information**
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu