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

KRAZATI 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg adagrasib.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white, oval shaped, film-coated tablet, approximately 8 x 16 mm, with a stylised "M" on one side and "200" marked on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KRAZATI as monotherapy is indicated for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with *KRAS* G12C mutation and disease progression after at least one prior systemic therapy.

4.2 Posology and method of administration

Treatment with KRAZATI should be initiated by a physician experienced in the use of anti-cancer medicinal products.

The presence of a *KRAS* G12C mutation must be confirmed using a validated test prior to initiation of therapy with KRAZATI.

Posology

The recommended dose of KRAZATI is 600 mg (three 200 mg tablets) twice daily.

Duration of treatment
Treatment with KRAZATI is recommended until disease progression or unacceptable toxicity.

Delayed or missed doses
Patients should be advised that if less than 4 hours have passed since the scheduled time of dosing, the patient should take the dose as normal. If a dose is missed by more than 4 hours, the dose should be skipped, and dosing should resume at the next scheduled dose. If vomiting occurs after taking a dose, patients should be advised not to take an additional dose. The next dose should be taken as prescribed.

Dose adjustments during treatment
The recommended dose reduction levels for the management of adverse reactions are outlined in Table 1.

Table 1: Recommended dose reduction levels for adverse reactions

Dose reduction level	Reduced dosage
First dose reduction	Two 200 mg tablets (400 mg) twice daily
Second dose reduction	Three 200 mg tablets (600 mg) once daily

The recommended dose modifications for adverse reactions are provided in Table 2. Severe (e.g., Grade 3) or intolerable adverse reactions require interruption of KRAZATI until sufficient improvement is observed before dosing is resumed.

Table 2: Recommended dosage modifications for adverse reactions

Adverse reaction	Severity[a]	Treatment modification
Nausea or vomiting despite appropriate supportive care (including anti-emetic therapy)	Grade 3 or 4	Withhold KRAZATI until recovery to ≤ Grade 1 or return to baseline Resume KRAZATI at the next lower dose level
Diarrhoea despite appropriate supportive care (including anti-diarrhoeal therapy)	Grade 3 or 4	Withhold KRAZATI until recovery to ≤ Grade 1 or return to baseline Resume KRAZATI at the next lower dose level
Hepatotoxicity	Grade 2 AST or ALT (3 to 5 times the ULN)	Decrease KRAZATI to the next lower level
	Grade 3 or 4 AST or ALT (> 5 times the ULN)	Withhold KRAZATI until recovery to ≤ Grade 1 or return to baseline Resume KRAZATI at the next lower dose level
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	Permanently discontinue KRAZATI
QTc Prolongation	Grade 3 (QTc ≥ 501 ms or > 60 ms change from baseline)	Withhold KRAZATI until recovery to ≤ Grade 1 or return to baseline Resume KRAZATI at the next lower dose level
	Grade 4 (ventricular arrhythmia)	Permanently discontinue KRAZATI
Other adverse reactions	Grade 3 or 4	Withhold KRAZATI until recovery to ≤ Grade 1 or return to baseline Resume KRAZATI at the next lower dose level

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal
[a] Grading defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

Special populations

Elderly population
No clinically relevant difference was observed among patients older and younger than 65 years of age. There are limited safety and efficacy data in patients 75 years or older. No dose adjustment is recommended (see Special populations in section 4.8).

Hepatic impairment
No clinically significant differences in the pharmacokinetics of adagrasib are expected in patients with mild to severe hepatic impairment (Child-Pugh classes A to C). No dose adjustment is recommended in patients with mild, moderate, or severe hepatic impairment (see section 5.2).

Renal impairment
No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment (see section 5.2).

Paediatric population
The safety and efficacy of adagrasib in children aged 0 to 18 years have not been established. No data are available (see section 5.1).

Method of administration

KRAZATI is for oral use. The tablets can be taken with or without food and should be swallowed whole with water. Administration with food may improve tolerability.

Administration to patients who have difficulty swallowing solids
Patients may disperse tablets in 120 mL of non-carbonated, room-temperature water, without crushing them. Other liquids must not be used. Patients should stir until the tablets are dispersed and drink immediately. The appearance of the mixture may be white with small pieces of the tablets that should not be chewed. The container must be rinsed with an additional 120 mL of water, which should be taken immediately.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Concomitant use of CYP3A substrates with a narrow therapeutic index (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

Gastrointestinal adverse reactions

Gastrointestinal (GI) adverse reactions including diarrhoea, nausea, and vomiting can occur with adagrasib (see section 4.8).

Patients should be monitored and managed using supportive care, including anti-diarrhoeals, antiemetics, or fluid replacement, as indicated. Based on the severity of the adverse reaction, the dose of KRAZATI should either be reduced, temporarily withheld until a return to ≤ Grade 1 or return to baseline then resumed at a reduced dose (see section 4.2).

Hepatotoxicity

Increased transaminases occurred in patients treated with adagrasib (see section 4.8).

Liver laboratory tests, including AST, ALT, alkaline phosphatase, and blood bilirubin should be monitored prior to the start of treatment and monthly for 3 months after starting treatment with KRAZATI and as clinically indicated, with more frequent testing in patients who develop transaminase and/or alkaline phosphatase elevations. Based on the severity of the adverse reaction, the adagrasib dose should either be reduced, temporarily withheld until a return to ≤ Grade 1 or return to baseline then resumed at a reduced dose or permanently discontinued. Specific guidance regarding dose management of KRAZATI in patients with increased transaminases is provided in section 4.2.

QT Prolongation

QTc interval prolongation can occur in patients treated with adagrasib (see section 4.8). It is recommended that a baseline electrocardiogram (ECG) prior to treatment initiation be performed in all patients and repeated during treatment.

When possible, the use of KRAZATI should be avoided in patients with congenital long QT syndrome, in patients with concurrent QTc prolongation and in patients who have experienced *torsades de pointes* arrhythmia in the past. Periodic monitoring with electrocardiograms and electrolytes should be considered in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products that are known to prolong the QTc interval. Based on the severity of the adverse reaction, and after correction of any possible electrolyte disturbances, treatment with KRAZATI can be continued with a reduced dose or temporarily discontinued followed by resumption at a reduced dose after a return to ≤ Grade 1 or return to baseline. In patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia, KRAZATI should be permanently discontinued (see sections 4.2, 4.5 and 4.8). The use of medicinal products known to prolong the QTc interval should be avoided (see section 4.5).

CYP3A substrates

Adagrasib is a strong CYP3A4 inhibitor. Co-administration of medicinal products that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated (e.g., alfuzosin, amiodarone, cisapride, pimozide, quinidine, ergotamine, dihydroergotamine, quetiapine, lovastatin, simvastatin, sildenafil, sirolimus, midazolam, triazolam, ticagrelor and tacrolimus).

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with KRAZATI.

Patients should be advised of the signs and symptoms and be monitored closely for skin reactions. If a SCAR is suspected, KRAZATI should be withheld, and the patient should be referred to a specialised unit for assessment and treatment. If SJS, TEN or DRESS related to adagrasib is confirmed, KRAZATI should be permanently discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies showed that adagrasib is metabolised primarily by CYP3A4 and is a reversible inhibitor of CYP2B6, CYP2C9, CYP2D6 and CYP3A4, as well as a time-dependent inhibitor of CYP3A4. *In vitro*, adagrasib is a substrate of BCRP and inhibits P-gp, BCRP, MATE-1/MATE-2K, OATP1B1, and OCT1.

Effects of other medicinal products on adagrasib

Strong CYP3A inducers
Co-administration of multiple doses of rifampicin 600 mg QD (strong CYP3A4 inducer) with a single 600 mg dose of adagrasib decreased adagrasib C_{max} by 88% and AUC by 95% in healthy subjects. Concomitant use of strong CYP3A inducers should be avoided.

Strong CYP3A inhibitors
Adagrasib C_{max} increased by 2.4-fold and AUC increased by 4-fold following concomitant use of a single dose of 200 mg (0.33 times the approved recommended dose) with itraconazole (a strong CYP3A inhibitor). Concomitant use of strong CYP3A inhibitors should be avoided.

Effects of adagrasib on other medicinal products

Substrates of cytochrome P450 (CYP) enzymes

CYP3A4 substrates: Coadministration of oral midazolam (a sensitive CYP3A4 substrate) with multiple doses of adagrasib (400 mg BID) increased midazolam AUC by approximately 21-fold in healthy subjects. Administration of multiple doses of adagrasib at 600 mg BID in patients is predicted to increase oral midazolam AUC by 31--foldAvoid concomitant use of adagrasib with sensitive CYP3A substrates unless otherwise recommended in the SmPC for these substrates.

CYP2C9 substrates: In vitro, adagrasib inhibits CYP2C9. Avoid concomitant use of adagrasib with sensitive CYP2C9 substrates where minimal concentration changes may lead to serious adverse reactions unless otherwise recommended in the SmPC for these substrates.

CYP2D6 substrates: Coadministration of dextromethorphan (a sensitive CYP2D6 substrate) with multiple doses of adagrasib (400 mg BID) increased dextromethorphan AUC by 1.8-fold in healthy subjects. Administration of adagrasib at 600 mg BID in patients is predicted to increase dextromethorphan AUC by 2.4-fold. Avoid concomitant use of adagrasib with sensitive CYP2D6 substrates where minimal concentration changes may lead to serious adverse reactions unless otherwise recommended in the SmPC for these substrates.

Transporter systems

P-glycoprotein (P-gp) substrates
Administration of adagrasib 600 mg single dose increased digoxin (a P-gp substrate) C_{max} and AUC by 1.1-fold and 1.4-fold, respectively, in healthy subjects. Avoid concomitant use of adagrasib with P-gp substrates where minimal concentration changes may lead to serious adverse reactions unless otherwise recommended in the SmPC for these substrates.

Breast cancer resistance protein (BCRP) or organic anion-transporting polypeptides 1B1 (OATP1B1) substrates
No clinically significant differences in the pharmacokinetics of rosuvastatin (a BCRP/OATP1B1 substrate) were observed when coadministered with adagrasib.

Medicinal products that prolong the QTc interval

The effect of co-administration of medicinal products known to prolong the QTc interval with adagrasib is unknown. The use of medicinal products known to prolong the QTc interval should be avoided. If concomitant administration of such medicinal products cannot be avoided, periodic ECG monitoring should be conducted (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception

Use of adagrasib is not recommended in women of childbearing potential not using contraception. Female patients of childbearing potential receiving adagrasib must use an effective contraceptive method during treatment and for at least 5 days following the last dose of adagrasib.

Pregnancy

There are no data from the use of adagrasib in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Adagrasib is not recommended during pregnancy.

Breast-feeding

There are no data on the presence of adagrasib or its metabolites in human milk, effects of adagrasib on the breast-fed child, or on milk production. A risk to breast-fed newborns/infants cannot be excluded. Adagrasib should not be used during breast-feeding.

Fertility

No clinical data are available on the possible effects of adagrasib on fertility.

4.7 Effects on ability to drive and use machines

Adagrasib has minor influence on the ability to drive and use machines. Dizziness (including vertigo and fatigue) may occur following administration of adagrasib (see section 4.8).
Patients should be advised that dizziness may occur and that, if affected, they should not drive, use machines, or take part in other activities where this would put themselves or others at risk.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions are diarrhoea (71.5%), nausea (68.1%), vomiting (57.7%), fatigue (57.3%), anaemia (33.5%), blood creatinine increased (31.5%), decreased appetite (30.0%), peripheral oedema (30.0%), AST increased (28.5%), ALT increased (27.7%), dizziness (21.5%), hyponatraemia (21.2%) and blood alkaline phosphatase increased (20.0%).

The most common severe adverse reactions (NCI CTCAE Grade $\geq$ 3) are anaemia (11.2%), fatigue (8.8%), hyponatraemia (6.2%), increased lipase (5.8%), lymphocyte count decreased (5.0%), electrocardiogram QT prolonged (5.0%), ALT increased (5.0%) and AST increased (5.0%).

The most common serious adverse reactions are blood creatinine increased (2.7%), hyponatraemia (2.7%), and nausea (2.3%).

Adverse reactions leading to treatment discontinuation are pneumonitis (< 1%), nausea (<1%), fatigue (<1%), ALT increased (<1%) and AST increased (<1%).

The most common adverse reactions leading to dose reduction or interruption are nausea (20.4%), fatigue (14.6%), diarrhoea (14.2%), vomiting (13.5%), ALT increased (11.2%), AST increased (9.2%), blood creatinine increased (6.2%), electrocardiogram QT prolonged (5.8%), and anaemia (5.0%).

Tabulated list of adverse reactions

Adverse reactions reported in clinical studies are listed by system organ class, preferred terms and by frequency.

Adverse reaction frequency estimates are derived from 260 patients exposed at adagrasib 600 mg twice-daily for a median duration of 7.3 months in pooled clinical studies involving patients with *KRAS* G12C mutation-positive, locally advanced, or metastatic NSCLC (n = 188), colorectal cancer (n = 46), and other solid tumours (n = 26). See section 5.1 for information on the characteristics of participants in the main clinical study.

The adverse reaction frequencies from clinical studies are displayed as all-cause adverse event frequencies; a proportion of the events included in the frequency estimate for an adverse reaction may have other causes, such as the disease being treated, concomitant medicinal products, or other unrelated causes.

Frequencies are defined as: 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions reported in patients treated with adagrasib

	All subjects treated with adagrasib 600 mg twice daily in clinical studies N = 260		
System organ class Adverse reaction	**Frequency category**	All Grades %	Grade ≥ 3 %
Blood and lymphatic system disorders			
Anaemia	Very common	33.5	11.2
Lymphocyte count decreased[1]	Very common	10.8	5.0
Metabolism and nutrition disorders			
Hyponatraemia	Very common	21.2	6.2
Decreased appetite	Very common	30.0	2.3
Nervous system disorders			
Dizziness[2]	Very common	21.5	1.5
Cardiac disorders			
Electrocardiogram QT prolonged	Very common	17.3	5.0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis	Common	5.4	1.9
Gastrointestinal disorders			
Diarrhoea	Very common	71.5	4.6
Nausea	Very common	68.1	4.2
Vomiting	Very common	57.7	1.9
Lipase increased	Very common	13.1	5.8
Amylase increased	Very common	11.9	< 1
Hepatobiliary disorders			
Hepatotoxicity[3]	Very common	39.2	7.7
Renal and urinary disorders			
Blood creatinine increased	Very common	31.5	< 1
General disorders and administration site conditions			
Fatigue[4]	Very common	57.3	8.8
Peripheral oedema	Very common	30.0	< 1

[1] Includes lymphocyte count decreased and lymphocytopenia
[2] Includes dizziness and vertigo
[3] Includes AST increased, ALT increased, blood alkaline phosphatase increased, blood bilirubin increased, Gamma-glutamyltransferase increased, hepatic enzyme increased, liver function test increased and mixed liver injury
[4] Includes fatigue and asthenia

Description of selected adverse reactions

Gastrointestinal adverse reactions

Gastrointestinal (GI) adverse reactions occur in 90.0% of patients taking adagrasib and include diarrhoea (71.5%, ≥G3 4.6%), nausea (68.1%, ≥G3 4.2%), and vomiting (57.7%, ≥ G3 1.9%). These events may lead to potential consequences such as dehydration, hyponatraemia, blood creatinine increased, and acute kidney injury.

Diarrhoea, nausea and vomiting resulted in dose interruption or reduction in 14.2%, 20.4% and 13.5% of patients respectively. Discontinuations due to nausea was 0.4%. No treatment discontinuations due to diarrhoea or vomiting were reported.

Hepatotoxicity
Hepatotoxicity-related reactions were reported in 39.2% (all grades) and 7.7% (Grade ≥ 3) of patients treated with adagrasib. Elevations of ALT occurred in 27.7% of patients and elevations of AST in 28.5% of patients. Grade ≥ 3 elevations of ALT and AST each occurred in 5.0% of patients. Liver injury has been reported in < 1% of patients. Median time to first onset of adverse reactions was 22 days for ALT and AST increased, 39.5 days for blood bilirubin increased and 25.5 days for blood alkaline phosphatase increased, with a median duration of 17, 15, 7.5 and 22 days, respectively.

Elevations of ALT resulted in dose interruption and/or reduction in 11.2% of patients, and elevations of AST resulted in dose interruption and/or reduction in 9.2% of patients. Discontinuations due to elevations of AST or ALT was 0.4% each.

QT prolongation
Corrected QT interval prolongation (QTcF) greater than 500 msec occurred in 6.6% of 257 patients with both baseline and on-study ECG assessments. Increase in QTcF interval > 60 msec from baseline occurred in 13.2% of patients. The median time to first onset of QT interval prolongation reported as a severe adverse event (CTCAE grade 3 and above) was 8 days with a median duration of 6 days.

QT interval prolongation resulted in dose interruption and/or reduction in 5.8% of patients (see sections 4.2 and 4.4). No QT interval prolongation leading to treatment discontinuation was observed.

Anaemia
Anaemia of any grade was reported in 33.5% of patients, with 11.2% of patients with grade ≥ 3 events. Median time to the first onset from first dose was 22 days, with a median duration of 31 days. Anaemia led to dose reduction or interruption in 5.0% of patients. No treatment discontinuation due to anaemia was reported.

Increased blood creatinine
Increased blood creatinine of any grade was reported 31.5% of patients, with < 1% of patients with grade ≥ 3 events. Median time to the first onset from first dose was 10.5 days, with a median duration of 23.0 days. Most cases were laboratory findings that did require intervention, and it remains unknown if these increases reflect a decrease in glomerular filtration rate. Blood creatinine may have also resulted from gastrointestinal fluid losses that may also be associated with dehydration and/or hyponatraemia.
Blood creatinine increased led to dose reduction or interruption in 6.2% of patients. No blood creatinine increased leading to treatment discontinuation was observed.

Hyponatraemia
Hyponatraemia was reported in 21.2% (all grades) and 6.2% (grade ≥ 3) of patients treated with adagrasib. Hyponatraemia led to dose reduction or interruption in 3.1% of patients. Median time to the first onset from first dose was 24 days, with a median duration of 15 days. No hyponatraemia leading to treatment discontinuation was observed.

Special populations

Elderly
Adagrasib has been studied in 117 patients aged ≥ 65-year-old. When compared to those < 65 years, no clinically relevant difference in safety profile was observed, except for fatigue (62.4% vs. 51.7%); decreased appetite (37.6% vs. 23.8%); and dizziness (27.4% vs. 15.4%).

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

In case of overdose, treatment should be interrupted, and general supportive measures initiated as appropriate. There is no specific antidote or treatment for adagrasib overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: L01XX77

Mechanism of action

Adagrasib is a selective, irreversible inhibitor of KRAS (Kirsten rat sarcoma viral oncogene homolog) G12C that covalently binds to the mutant cysteine in KRAS G12C and locks the mutant KRAS protein in its inactive, GDP-bound conformation, which prevents KRAS-dependent downstream signalling. Adagrasib inhibits tumour cell growth and viability in cells harbouring *KRAS* G12C mutations and results in regression in *KRAS* G12C-positive nonclinical tumour models with minimal off-target activity.

Cardiac electrophysiology
Based on the concentration-QTcF relationship, the mean (90 % CI) QTcF change from baseline (ΔQTcF) was 17.93 ms (15.13 – 20.73 ms) at the population geometric mean steady-state maximum concentration ($C_{max,ss}$) in patients after administration of adagrasib 600 mg twice daily.

Clinical efficacy and safety

The efficacy of adagrasib was evaluated in KRYSTAL-1 (Study 849-001), a multicentre, single arm, open-label multiple expansion cohort study. Patients with locally advanced or metastatic NSCLC with *KRAS* G12C mutation who previously received treatment with a platinum-based regimen and an immune checkpoint inhibitor were enrolled into the pivotal efficacy cohort, Cohort A. Identification of a *KRAS* G12C mutation was prospectively determined in tumour tissue by local laboratories using next generation sequencing (NGS), polymerase chain reaction (PCR) or Sanger sequencing. Patients with active brain metastases, carcinomatous meningitis, history of recent significant haemoptysis or haemorrhage, or prior treatment with a *KRAS* G12C inhibitor were excluded from the pivotal cohort. Patients received adagrasib 600 mg orally twice daily as monotherapy until unacceptable toxicity or disease progression.

The primary efficacy endpoint for Cohort A was objective response rate (ORR) in accordance with RECIST v1.1, and duration of response (DOR), was a secondary endpoint. Both endpoints were evaluated using blinded independent central review.

A total of 116 patients were enrolled and treated with adagrasib for a median of 5.7 months and a mean of 7.0 months.

The median age was 64.0 years (range: 25 to 89 years); 56.0% were female; 83.6% were White; 7.8% were Black; 4.3% were Asian, and 4.3% were other. Eastern Cooperative Oncology Group (ECOG) performance status was 0 (15.5%) or 1 (83.6%). Tumour histology was adenocarcinoma for 97.4% of patients, and 88.8% of patients had metastatic disease. Patients received a median of 2 prior systemic therapies (range: 1 to 7); 43.1% received 1 line, 34.5% received 2 lines, 10.3% received 3 lines, and 12.1% received 4 or more lines; 98.3% received both prior platinum and prior anti-PD-1/PD-L1 therapy. Sites of disease included lung 86.2%, lymph node 58.6%, bone 43.1%, brain 29.3%, liver 20.7%, adrenals 19.8%, and other 30.2%.

Efficacy results are summarised in Table 4.

Table 4: Efficacy results for patients with advanced *KRAS* G12C-mutant NSCLC previously treated with platinum chemotherapy and an immune checkpoint inhibitor in KRYSTAL-1

Endpoint	Adagrasib (n = 116)
Objective response rate (95% CI)[a,b]	41.4 (32.3, 50.9)
Complete response rate, %	0.9
Partial response rate, %	40.5
Duration of response[a,b]	
Number of patients with an objective response	48
Median in months (95% CI)	8.5 (6.2, 13.8)
Proportion of responses ≥ 6 months, %[c]	58.3

CI = Confidence interval
[a] Assessed by Blinded Independent Central Review (BICR)
[b] Based on 15 October 2021 data cut
[c] Observed proportion of patients with duration of response beyond landmark time

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with adagrasib in all subsets of the paediatric population for treatment of all solid and haematological malignancies (see section 4.2 for information on paediatric use).

Conditional marketing authorisation

This medicinal product has been authorised under the 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

The pharmacokinetics of adagrasib have been characterised in healthy subjects and in patients with *KRAS* G12C-mutation. Adagrasib AUC and C_{max} increase dose proportionally over the dose range of 400 mg to 600 mg. With a 600 mg twice daily dosing regimen in patients, adagrasib steady state was reached within 8 days of dosing, and adagrasib accumulated approximately 6-fold relative to a single dose.

Absorption

The absolute oral bioavailability of adagrasib is unknown. The median T_{max} of adagrasib is approximately 6 hours.

Effect of food
No clinically significant differences in the pharmacokinetics of adagrasib were observed following administration of a high-fat and high-calorie meal.

Distribution

The geometric mean (CV%) apparent volume of distribution of adagrasib (Vz/F) in healthy subjects is 942 L (57%). Human plasma protein binding of adagrasib is approximately 99%.

Elimination

Based on a population PK analysis, the estimated terminal elimination half-life ($t_{1/2}$) and apparent oral clearance (CL/F) at steady state in patients are approximately 29 hours and 25.8 L/h, respectively.

Metabolism

Adagrasib is metabolised primarily by CYP3A4 and inhibits its own CYP3A4 metabolism.

Excretion

Following a single oral dose of radiolabelled adagrasib, approximately 75% of the dose was recovered in faeces and 4.5% recovered in urine.

Special populations

Based on a population pharmacokinetic analysis, no clinically meaningful differences in the pharmacokinetics of adagrasib were observed based on age (19 to 89 years), sex, race (White, Black and Asian), body weight (36 to 139 kg), ECOG PS (0, 1), or tumour burden. No clinically significant differences in the pharmacokinetics of adagrasib are expected in patients with mild to severe renal impairment (CLcr 15 to < 90 mL/min estimated by Cockcroft-Gault equation) or in patients with mild to severe hepatic impairment (Child-Pugh classes A to C).

5.3 Preclinical safety data

Repeat dose toxicity

In repeat dose non-clinical safety studies with adagrasib, early deaths occurred in rats at dose ≥ 300 mg/kg/day (human equivalent dose of 2 900 mg/day). In animals that survived, the primary finding in rats and dogs was reversible phospholipidosis in multiple organs. In the rat, the target tissues included lung, trachea, heart, skeletal muscle, bone marrow, spleen, pancreas and female sex organs. In the dog, target tissues included bone marrow, lung, heart and spleen. The extent of vacuolation and the presence of foamy macrophages were more prominent in the rat as compared to dog, and these effects occurred at systemic exposures (based on AUC) below those in humans administered adagrasib at 600 mg twice daily in both species. The no observed adverse effect level in the 13-week rat and dog study was 150 mg/kg/day (human equivalent dose of 1 450 mg/day) and 15 mg/kg (human equivalent dose of 600 mg/day), respectively.

Genotoxicity / Carcinogenicity

Adagrasib was not mutagenic or genotoxic in a battery of *in vitro* and *in vivo* assays. Carcinogenicity studies have not been conducted with adagrasib.

Reproductive toxicity

Dedicated fertility studies with adagrasib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, there was evidence of vacuolation in female sex organs that was suggestive of phospholipidosis, which reversed after cessation of dosing and was not considered adverse.

Adagrasib administration to pregnant rats at doses up to 270 mg/kg/day (human equivalent dose of 2 600 mg/day) during periods of organogenesis led to maternal toxicities, however at 90 mg/kg/day (human equivalent dose of 870 mg/day) there were no adverse effects on maternal or foetal development. In rabbits, at doses of 30 mg/kg/day (human equivalent dose of 580 mg/day) there were no adverse effects on dams and foetuses. Higher doses in rabbits led to maternal toxicities and embryofoetal lethality. In both the rat and rabbit studies, the exposures associated with no adverse

effect dose levels were lower (less than 1-fold) compared to those obtained in humans at the clinical dose of 600 mg twice daily.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose (E 460)
Mannitol (E 421)
Crospovidone
Silica, colloidal anhydrous (E 551)
Magnesium stearate (vegetable)

Film-coating
Hypromellose
Titanium dioxide (E 171)
Polydextrose (E 1200)
Talc (E 553b)
Maltodextrin
Medium chain triglycerides (vegetable)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 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.
Keep the bottle tightly closed.

6.5 Nature and contents of container

Each carton contains one white opaque HDPE bottle with a white, child resistant polypropylene closure and an aluminium foil heat induction seal. Each HDPE bottle contains two 1 g of silica gel desiccant containers.

Pack sizes: bottles with 120 and 180 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

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2

Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1744/001
EU/1/23/1744/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 05 January 2024

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. MANUFACTURER 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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Manufacturing Packaging Farmaca (MPF) B.V.
Neptunus 12
8448 CN Heerenveen
Netherlands

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 Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

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 medicinal 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.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy and safety of adagrasib in the treatment of patients with *KRAS* G12C-mutated NSCLC, the MAH should submit the clinical study report for the phase 3 clinical study KRYSTAL-12, comparing adagrasib versus docetaxel for the treatment of previously treated patients with *KRAS* G12C mutated NSCLC. The clinical study report will be submitted by:	Q3/2024

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

KRAZATI 200 mg film-coated tablets
adagrasib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 200 mg adagrasib.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

120 film-coated tablets
180 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. Keep the bottle tightly closed.

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

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/23/1744/001 120 film-coated tablets
EU/1/23/1744/002 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

KRAZATI 200 mg [Outer packaging only]

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included. [Outer packaging only]

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN [Outer packaging only]

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

KRAZATI 200 mg film-coated tablets
adagrasib

▼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 KRAZATI is and what it is used for

KRAZATI contains the active substance adagrasib and belongs to a group of medicines known as antineoplastic agents, cancer medicines.

KRAZATI is used to treat adults with a type of lung cancer called non-small cell lung cancer (NSCLC) when it is advanced or has spread to other parts of the body.

KRAZATI is used when previous treatments were not effective in stopping the growth of the cancer, and when the cancer cells have mutations (changes) that allow them to produce an abnormal form of a protein called KRAS G12C. Your doctor will test for this change in your cancer cells beforehand to make sure that KRAZATI is right for you.

How does KRAZATI work?

The abnormal KRAS G12C protein makes the cancer cells grow out of control. The active substance in KRAZATI, adagrasib, attaches to this abnormal protein and stops it from working, which may slow down or stop the growth of the cancer.

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

2. What you need to know before you take KRAZATI

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

- if you are taking any of the following medicines as they may cause serious and/or life-threatening side effects:
  - alfuzosin (used to treat benign prostatic hyperplasia)
  - amiodarone (used to treat heart problems)
  - cisapride (used to treat symptoms of night time heartburn and other gastrointestinal disorders
  - pimozide, quetiapine (antipsychotic medicines)
  - quinidine (used to treat malaria and heart problems)
  - ergotamine, dihydroergotamine (used to treat migraines)
  - lovastatin, simvastatin (used to lower cholesterol levels)
  - sildenafil (for the treatment of pulmonary arterial hypertension)
  - triazolam (used to treat insomnia)
  - sirolimus, tacrolimus (used to prevent rejection of transplanted organs)
  - ticagrelor (used to prevent heart attack and stroke)

Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking KRAZATI.

KRAZATI may affect your liver. Your doctor may carry out some tests before you begin taking KRAZATI, once a month for the first 3 months of your treatment and as considered necessary by your doctor. Based on the results of these tests, your dose of KRAZATI may be either reduced, interrupted, or stopped.

Talk to your doctor **before** you take KRAZATI if you:
- have heart or circulatory problems,
- experience or have experienced abnormal electrical activity of the heart that affects its rhythm or
- take any heart medicines that carry a risk of heart rhythm problems, see "**Other medicines and KRAZATI**"

Your doctor will decide if this medicine is suitable for you and may monitor your heart with an electrocardiogram (ECG; a test which measures the electrical activity of the heart) and adjust your dose of KRAZATI accordingly.

Talk to your doctor **during** your treatment if you:
- develop problems such as diarrhoea, feeling sick (nausea), and vomiting. Your doctor may decide to reduce or interrupt the dose or stop treatment with KRAZATI.
- feel dizzy or develop any heart problems such as a fast or irregular heartbeat.

Serious and potentially fatal skin reactions (such as Stevens–Johnson syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms) have been reported in association with KRAZATI.

Stop using KRAZATI and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions (which may include reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes, widespread rash, and enlarged lymph nodes. These serious skin rashes can be preceded by fever and flu-like symptoms).

Children and adolescents

KRAZATI has not been studied in children or adolescents. Treatment with KRAZATI is not recommended in persons under 18 years of age.

Other medicines and KRAZATI

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal supplements and medicines obtained without prescription. This is because KRAZATI can affect how some other medicines work, and some other medicines can affect how KRAZATI works.

See '**Do not take KRAZATI'** if you are taking any medicines that might interact with KRAZATI.

Certain medicines and herbal supplements may reduce how well KRAZATI works by decreasing the amount of KRAZATI in the blood. These medicines include:
- Rifampicin (used to treat tuberculosis and other infections)
- Carbamazepine, phenobarbital, phenytoin (used to treat epilepsy)
- St John's Wort (*Hypericum perforatum*; available as either a medicine or a herbal supplement and is used to treat depression)

Certain medicines may increase the risk of side effects of KRAZATI by increasing the levels of KRAZATI in the blood. These medicines include:
- Itraconazole, ketoconazole. posaconazole, or voriconazole (used to treat fungal infections)
- Clarithromycin, telithromycin, or troleandomycin (used to treat bacterial infections)
- Ritonavir (used with other medications to treat HIV infection)

KRAZATI may increase the side effects of some medicines by increasing the amount of these medicines in the blood. Examples of these medicines include:
- Warfarin (used to treat blood clots). Your doctor may need to monitor the time your blood takes to clot (prothrombin time or INR test).

Some medicines may cause a change in the electrical conduction in your heart, particularly when taken with KRAZATI. Examples include:
- some medicines for heart rhythm disorders (e.g. amiodarone, disopyramide, dofetilide, dronedarone, flecainide, hydroquinidine, ibutilide, nifekalant, procainamide, quinidine, sotalol)
- some medicines to treat bacterial or fungal infections (e.g. azithromycin, ciprofloxacin, clarithromycin, erythromycin, levofloxacin, moxifloxacin, roxithromycin, fluconazole) or malaria (e.g. chloroquine, halofantrine, hydroxychloroquine)
- some medicines used to treat gastrointestinal disorders (e.g., chlorpromazine, domperidone, droperidol, and ondansetron for nausea; loperamide for diarrhoea)
- some medicines used to treat schizophrenia and mood disorders (e.g. chlorprothixene, citalopram, escitalopram, haloperidol, sulpiride)
- others (e.g. anagrelide and cilostazol to prevent blood clots; bepridil for high blood pressure; donepezil for Alzheimer's disease; methadone for pain and opioid addiction; pimozide for tics associated with Tourette's Disorder; terfenadine for allergic rhinitis; terodiline for bladder incontinence)

Talk with your doctor if you are taking these or any other medicines.

KRAZATI with food and drink

Drinking certain brands of grapefruit juice and in large amounts whilst you start taking KRAZATI may increase your chance of getting side effects by increasing the levels of KRAZATI in the blood.

Pregnancy

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Do not take KRAZATI if you are pregnant, or suspect you are pregnant, unless advised by your doctor. The effects of KRAZATI in pregnant women are not known.

Contraception

Women who can become pregnant must use an effective method of contraception to avoid becoming pregnant during treatment with KRAZATI and for at least 5 days following the last dose. Talk to your doctor about the most suitable contraception for you.

Breast-feeding

Do not breast-feed your baby whilst you are being treated with KRAZATI. It is not known if this medicine passes to the baby via breast milk.

Driving and using machines

KRAZATI has a minor influence on the ability to drive and use machines. If you feel dizzy, a spinning sensation or tiredness do not drive, use machines or take part in activities where this puts yourself or others at risk.

3. How to take KRAZATI

You will be prescribed this medicine by a doctor experienced in the use of anti-cancer medicines. Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The recommended dose is **three 200 mg tablets (600 mg in total) taken twice daily**.

Do not change your dose unless your doctor or pharmacist tells you to.
Your doctor may decrease the dose or stop your medicine depending on how well you tolerate it.

How to take
Take the medicine at the same time each day.
You can take the medicine with or without food.
Swallow the tablets whole with water.

If you cannot swallow tablets whole:
- Place your dose of KRAZATI in half a glass (not less than 120 mL) of still, room temperature drinking water, without crushing the tablets. Do not use any other liquids, including acidic beverages (e.g. fruit juices).
- Swirl gently until the mixture looks white with small pieces of tablet. Do not to chew the pieces.
- Drink the mixture immediately.
- Rinse the glass with an additional half a glass of water and drink it immediately to make sure that you have taken the full dose of KRAZATI.

If you take more KRAZATI than you should

Contact your doctor, pharmacist or nurse immediately if you take more tablets than recommended.

If you vomit after taking KRAZATI

If you vomit after taking a dose, do not take an extra dose. Take your next dose at your next scheduled time.

If you forget to take KRAZATI

If you miss a dose, take it as soon as possible. If you miss your dose by more than 4 hours, skip that dose and take your usual dose at the next scheduled time. Do not take a double dose to make up for a forgotten dose.

If you stop taking KRAZATI

Do not stop taking this medicine. Talk to your doctor first. It is important to take this medicine every day, for as long as your doctor tells you to.

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

4. Possible side effects

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

Very common (may affect more than 1 in 10 people) and serious possible side effects of KRAZATI are:

- QT prolongation, a heart conduction abnormality that can lead to a life-threatening heart rhythm

  Tell your doctor immediately if you develop:
  - chest pain
  - shortness of breath
  - a fast heart rate or pounding heartbeat.

  Your doctor may monitor your heart with an ECG (electrocardiogram) and may decide to either reduce the dose of KRAZATI or stop your treatment (see section 2).

- Increased levels of certain liver enzymes (ALT, AST) and bilirubin (a substance in the liver that can cause yellowing of the skin and eyes) are signs of liver problems. Your doctor should do blood tests to check how well your liver is working and may decide to either reduce or interrupt the dose or stop treatment with KRAZATI (see section 2).

Other possible side effects of KRAZATI may include:

Very common (may affect more than 1 in 10 people)
- low levels of red blood cell counts (anaemia) which can cause tiredness and pale skin
- low levels of lymphocytes (a type of white blood cell; lymphocytopenia)
- low blood sodium levels which can cause headache, tiredness, fits and coma
- loss of appetite
- feeling dizzy, a spinning sensation
- a sign of worsening kidney problems (creatinine increased)
- feeling sick (nausea)
- diarrhoea
- vomiting
- Abnormal blood test results indicate high levels of lipase and/or amylase in your blood stream
- tiredness, weakness
- swelling especially of the ankles and feet due to fluid retention

Common (may affect up to 1 in 10 people)
- inflammation in the lungs causing shortness of breath and cough (pneumonitis)

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 KRAZATI

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 bottle label and carton after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture. Keep the bottle tightly closed.

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 KRAZATI contains
- The active substance is adagrasib. Each film-coated tablet contains 200 mg adagrasib.
- The other ingredients are:
  Tablet core
  Microcrystalline cellulose (E 460), mannitol (E 421), crospovidone, silica colloidal anhydrous (E 551), magnesium stearate (vegetable).
  Film-coating
  Hypromellose, titanium dioxide (E 171), polydextrose (E 1200), talc (E 553b), maltodextrin, medium chain triglycerides (vegetable).

What KRAZATI looks like and contents of the pack
KRAZATI film-coated tablets are white to off-white and oval shaped, with a stylised 'M' on one side and '200' marked on the other side.

The medicine comes in white opaque plastic bottles with white, child resistant lid and a heat-induction seal. Each bottle contains two silica gel desiccant packets which must be kept in the bottle to help protect your tablets from moisture. They must not be swallowed.

The pack sizes are bottles with either 120 or 180 film-coated tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
Manufacturing Packaging Farmaca (MPF) B.V.
Neptunus 12
8448 CN Heerenveen
Netherlands

This leaflet was last revised in month YYYY.

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

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

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.