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

LUMYKRAS 120 mg film-coated tablets
LUMYKRAS 240 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LUMYKRAS 120 mg film-coated tablets
Each film-coated tablet contains 120 mg of sotorasib.

Excipient with known effect
Each film-coated tablet contains 114 mg of lactose (as monohydrate).

LUMYKRAS 240 mg film-coated tablets
Each film-coated tablet contains 240 mg of sotorasib.

Excipient with known effect
Each film-coated tablet contains 53 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

LUMYKRAS 120 mg film-coated tablets

Yellow film-coated tablet, oblong-shaped (7 mm × 16 mm), debossed with “AMG” on one side and “120” on the opposite side.

LUMYKRAS 240 mg film-coated tablets

Yellow film-coated tablet, oval-shaped (8 mm × 18 mm), debossed with “AMG” on one side and “240” on the opposite side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LUMYKRAS as monotherapy is indicated for the treatment of adults with advanced non-small cell lung cancer (NSCLC) with *KRAS G12C*-mutation and who have progressed after at least one prior line of systemic therapy.

4.2 Posology and method of administration

Treatment with LUMYKRAS must be initiated by a physician experienced in the use of anticancer medicinal products.

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

Posology

The recommended dose is 960 mg sotorasib (eight 120 mg tablets or four 240 mg tablets) once daily, at the same time each day.

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

Missed doses or vomiting
If less than 6 hours have passed since the scheduled time of dosing, the patient should take the dose as normal. If more than 6 hours have passed since the scheduled time of dosing, the patient must not take the dose. Treatment should be continued as prescribed the next day.

If vomiting occurs after taking LUMYKRAS, the patient must not take an additional dose on the same day, and treatment must be continued as prescribed the next day.

Dose modifications
Dosing should be modified based on LUMYKRAS toxicity. The dose reduction rules outlined in section 4.2 are based on clinical data. Pharmacokinetic (PK) data do suggest a similar exposure at lower sotorasib doses (see section 5.2). Dose reduction levels are summarised in table 1. Dose modifications for adverse reactions are provided in table 2.

A maximum of two dose reductions are recommended for management of an adverse reaction (see table 1). Discontinue LUMYKRAS if an adverse reaction cannot be managed after two dose reductions and patients are unable to tolerate the minimum dose of 240 mg once daily.

Table 1. Recommended sotorasib dose reduction levels

Dose reduction level	**Dose**
Starting dose	960 mg (eight 120 mg tablets or four 240 mg tablets) once daily
First dose reduction	480 mg (four 120 mg tablets or two 240 mg tablets) once daily
Second dose reduction	240 mg (two 120 mg tablets or one 240 mg tablet) once daily

Table 2. Recommended dose modifications for sotorasib

Adverse reaction	Severity[a]	Dose modification
Hepatotoxicity	AST or ALT > 3 × and up to 5 × ULN (or > 3 × and up to 5 × baseline if baseline abnormal) with symptoms or AST or ALT > 5 × ULN (or > 5 × baseline if baseline abnormal), in the absence of alternative causes.	• Withhold treatment • Closely monitor liver function until recovered to ≤ 3 × ULN or to ≤ 3 × baseline if baseline abnormal. • After recovery, resume treatment at the next dose reduction level • Consider initiation of corticosteroids
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN or AST or ALT > 3 × ULN and INR > 1.5 × ULN (for subjects not on anticoagulation therapy), in the absence of alternative causes.	• Permanently discontinue treatment if no alternative cause is identified. • If alternative cause is identified, do not resume treatment until AST/ALT/bilirubin return to baseline.
Interstitial Lung Disease (ILD)/pneumonitis	Any grade	• Stop treatment if ILD/pneumonitis is suspected • Permanently discontinue treatment if ILD/pneumonitis is confirmed and no other cause is identified.
Nausea, vomiting, or diarrhoea persisting despite supportive care (including anti-emetic or anti-diarrhoeal therapy)	Grade ≥ 3	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level
Other medicinal product-related toxicity	Grade ≥ 3	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction 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; INR = International Normalised Ratio

Special populations

Elderly
The limited data on the safety and efficacy of LUMYKRAS in patients aged 75 years and older do not suggest that a dose adjustment is required in elderly patients (see sections 4.8 and 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild hepatic impairment.

LUMYKRAS is not recommended for use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment (see section 5.2).

Renal impairment
No dose adjustment is recommended for patients with mild renal impairment (creatine clearance, CrCL ≥ 60 mL/min). LUMYKRAS has not been studied in patients with moderate or severe renal impairment (CrCL < 60 mL/min). Therefore, caution should be exercised when treating patients with moderate, severe and end stage renal impairment (see section 5.2).

Paediatric population
There is no relevant use of LUMYKRAS in the paediatric population in the treatment of non-small cell lung cancer.

Method of administration

LUMYKRAS is for oral use. The tablets must be swallowed whole. There are no data to support the administration of LUMYKRAS if the tablets are chewed, crushed, or split but the tablets can be dispersed in water (see below). The tablets can be taken with or without food.

Administration to patients who have difficulty swallowing solids
Patients should 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 into small pieces (the tablet will not dissolve completely) and drink it immediately. The appearance of the mixture may range from pale to bright yellow. The container must be rinsed with an additional 120 mL of water, which should be drunk immediately. If it is not drunk immediately, patients must stir again to ensure that the tablets are dispersed. The dispersion must be discarded if it is not drunk within 2 hours.

If administration through a nasogastric (NG) tube or percutaneous endoscopic gastrostomy (PEG) tube is required, follow the process above for the initial dispersion and for the residual rinse of the 120 mg or 240 mg tablets. The dispersed suspension and rinse should be administered as per the NG or PEG tube manufacturer's instructions with appropriate water flushes. Administer the dispersion within 2 hours of preparation, stored at room temperature.

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

Hepatotoxicity

Sotorasib can cause hepatotoxicity, which may lead to drug-induced liver injury (DILI) and hepatitis. Sotorasib has been associated with transient elevations of serum transaminases (ALT and AST), alkaline phosphatase and total bilirubin in 960 mg monotherapy clinical trials. In a total of 740 patients with *KRAS G12C*-mutated solid tumours who received LUMYKRAS 960 mg monotherapy daily, the incidence for hepatotoxicity is highest in the sub-group of patients with recent (≤ 3 months) immunotherapy (38%) prior to starting LUMYKRAS, as compared to those who started LUMYKRAS either more than 3 months after last dose of immunotherapy (17%) or those who never received immunotherapy (22%). Regardless of time from prior immunotherapy, 87% of elevations improved or resolved with interruption of LUMYKRAS treatment and treatment with corticosteroids. Elevated liver enzymes led to discontinuation of treatment in 10%, 2% and 0% of patients with prior immunotherapy within ≤ 3 months, with prior immunotherapy within > 3 months and no prior immunotherapy, respectively. Among 740 patients with *KRAS G12C*-mutated solid tumours who received 960 mg orally once daily, 26% experienced hepatotoxicity and 13% had hepatotoxicity leading to dose interruption and/or dose reduction. Overall, 41% of patients with hepatotoxicity

received concurrent corticosteroids. Cases of liver enzyme increase can be asymptomatic. Patients should be monitored for liver function (ALT, AST, alkaline phosphatase and total bilirubin) prior to the start of LUMYKRAS, every 3 weeks for the first 3 months of treatment, then once a month or as clinically indicated, with more frequent testing in patients with recent immunotherapy and in patients with serious hepatotoxicity events. Based on the severity of the laboratory abnormalities, treatment with LUMYKRAS must be interrupted until recovered to ≤ 3 × ULN or to ≤ 3 baseline (if baseline abnormal) and treatment with corticosteroids considered, and the dose of LUMYKRAS must be either modified or permanently discontinued (see section 4.2).

Interstitial Lung Disease (ILD)/pneumonitis

LUMYKRAS can cause ILD/pneumonitis that can be fatal. ILD/pneumonitis occurred in patients treated with LUMYKRAS with prior exposure to immunotherapy or radiotherapy (see section 4.8). Recent (≤ 3 months) immunotherapy prior to starting LUMYKRAS may be considered a risk factor for ILD/pneumonitis. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g. dyspnoea, cough, fever). Immediately withhold LUMYKRAS in patients with suspected ILD/pneumonitis and permanently discontinue LUMYKRAS if no other causes of ILD/pneumonitis are identified (see section 4.2).

Use in population with hepatic impairment

There are no data on the clinical safety and efficacy of multiple doses of LUMYKRAS when administered to patients with moderate and severe hepatic impairment (Child-Pugh B and C). No dose recommendation can be made.

Lactose intolerance

LUMYKRAS contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

In vitro studies indicate that sotorasib is metabolised by cytochrome P450 (CYP) 2C8, CYP3A4, and CYP3A5, and is a substrate of P-glycoprotein (P-gp). Sotorasib was an inducer of CYP3A4, CYP2B6, CYP2C8, CYP2C9, and CYP2C19 *in vitro*. Sotorasib is an *in vitro* inhibitor of CYP2C8, CYP2D6, and CYP3A. *In vitro* studies indicate that sotorasib is an inhibitor of human organic anion transporter (OAT)1/3, OATP1B1, Breast Cancer Resistance Protein (BCRP) and P-gp.

Effects of other medicinal products on sotorasib

Acid-reducing agents
Co-administration of sotorasib with a PPI (omeprazole) or an H_2 receptor antagonist (famotidine) led to a decrease in sotorasib concentrations.

Under fed conditions (standard-calorie moderate-fat meals), co-administration of multiple doses of omeprazole with a single dose of 960 mg sotorasib decreased sotorasib C_{max} by 65% and area under the curve (AUC) by 57%. Co-administration of a single dose of famotidine given 10 hours prior and 2 hours after a single dose of 960 mg sotorasib decreased sotorasib C_{max} by 35% and AUC by 38%.

Under fasted conditions, co-administration of multiple doses of omeprazole with a single dose of 960 mg sotorasib decreased sotorasib C_{max} by 57% and AUC by 42%. Under fasted conditions, co-administration of repeat doses of omeprazole with a single dose of 960 mg sotorasib and 240 mL of

an acidic beverage (non-diet cola) decreased sotorasib C_{max} by 32% and AUC by 23%. The clinical relevance of the decreased sotorasib exposure when co-administered with omeprazole and cola is unclear and efficacy might be reduced.

If co-administration of LUMYKRAS with an acid-reducing agent (such as a PPI or an H_2 receptor antagonist) is required, LUMYKRAS should be taken with an acidic beverage (such as cola). Alternatively, LUMYKRAS should be taken 4 hours before or 10 hours after administration of a local antacid.

CYP3A4 inhibitors
Co-administration of multiple dose itraconazole (a strong CYP3A4 and P-gp inhibitor) did not increase sotorasib exposures to a clinically significant extent. No dose adjustment of LUMYKRAS is recommended when co-administered with CYP3A4 inhibitors.

Strong CYP3A4 inducers
Co-administration of sotorasib with multiple doses of a strong CYP3A4 inducer (rifampicin) decreased sotorasib C_{max} by 35% and AUC by 51%. Co-administration of strong CYP3A4 inducers (e.g. rifampicin, carbamazepine, enzalutamide, mitotane, phenytoin and St. John's wort) with LUMYKRAS is not recommended because they may decrease sotorasib exposure.

Effect of sotorasib on other medicinal products

CYP3A4 substrates
Sotorasib is a moderate CYP3A4 inducer. Co-administration of sotorasib with CYP3A4 substrates led to a decrease in their plasma concentrations, which may reduce the efficacy of these substrates.

Co-administration of sotorasib with midazolam (a sensitive CYP3A4 substrate) decreased midazolam C_{max} by 48% and AUC by 53%.

Avoid co-administration of LUMYKRAS with CYP3A4 substrates with narrow therapeutic indices, including but not limited to alfentanil, ciclosporin, dihydroergotamine, ergotamine, fentanyl, hormonal contraceptives, pimozide, quinidine, sirolimus, tacrolimus, amlodipine and manidipine. If co-administration cannot be avoided, adjust the CYP3A4 substrate dose in accordance with the current summary of product characteristics.

CYP2B6, CYP2C8, CYP2C9 and CYP2C19 substrates
In vitro data indicated that sotorasib may have the potential to induce CYP2B6, CYP2C8, CYP2C9 and CYP2C19; the clinical relevance of these findings is unknown. When sotorasib is co-administered with medicinal products metabolised by these enzymes, appropriate monitoring is recommended.

CYP2D6 substrates
In vitro data indicated that sotorasib may have the potential to inhibit CYP2D6, the clinical relevance of these findings is unknown. When LUMYKRAS is co-administered with CYP2D6 substrates (e.g. flecainide, propafenone, metoprolol), appropriate monitoring is recommended.

BCRP substrates
LUMYKRAS is a weak BCRP inhibitor. Co-administration of LUMYKRAS with a BCRP substrate led to an increase in the plasma concentrations of the BCRP substrate, which may increase the effect of the substrate.

Co-administration of LUMYKRAS with rosuvastatin (a BCRP substrate) increased the rosuvastatin C_{max} by 70% and AUC by 34%.

When LUMYKRAS is co-administered with a BCRP substrate, including but not limited to lapatinib, methotrexate, mitoxantrone, rosuvastatin and topotecan, monitor for adverse reactions of the BCRP substrate and reduce the BCRP substrate dose in accordance with its current summary of product characteristics.

Effect of sotorasib on P-gp substrates
Co-administration of sotorasib with digoxin (a P-glycoprotein [P-gp] substrate) increased digoxin C_{max} by 1.9-fold and AUC_{inf} by 1.2-fold of digoxin administered alone. Co-administration of LUMYKRAS with P-gp substrates with narrow therapeutic indices is not recommended. If co-administration cannot be avoided, adjust the P-gp substrate dosage in accordance with the current summary of product characteristics.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential must be advised to avoid pregnancy while on LUMYKRAS. Female patients of childbearing potential receiving LUMYKRAS must use highly effective contraceptive methods during treatment and for at least 7 days following the last dose of LUMYKRAS. LUMYKRAS may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method.

Pregnancy

There are no data from the use of sotorasib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). LUMYKRAS is not recommended during pregnancy and in women of childbearing potential not using contraception. Patients must be informed of the potential hazards to the foetus if LUMYKRAS is used during pregnancy, or if the patient becomes pregnant while taking LUMYKRAS.

Breast-feeding

It is unknown if sotorasib or its metabolites are excreted in human milk. A risk to breast-fed newborns/infants cannot be excluded. LUMYKRAS should not be used during breast-feeding.

Fertility

There are no clinical studies to evaluate the effect of sotorasib on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Adverse drug reactions (ADRs) described in table 3 reflect exposure to sotorasib 960 mg once daily as monotherapy in 740 patients with *KRAS G12C*-mutated solid tumours across multiple clinical studies, including CodeBreaK 200, CodeBreaK 100 phase 2 part A, and CodeBreaK 100 phase 2 part B (dose comparison sub-study) and three phase 1 studies.

The most common adverse reactions in patients treated with LUMYKRAS 960 mg once daily were diarrhoea (36.6%), nausea (24.7%), fatigue (19.1%), vomiting (16.1%), arthralgia (15.3%), and decreased appetite (15.1%). The most common severe (grade ≥ 3) adverse reactions were diarrhoea (6.9%), increased ALT (5.9%) and increased AST (4.6%). The most common adverse reactions leading to permanent discontinuation of treatment were increased ALT (1.5%) and increased AST (1.1%) and DILI (1%). The most common adverse reactions leading to dose modification were diarrhoea (11.4%), increased ALT (5.9%), increased AST (5.7%), nausea (3.8%), increased blood alkaline phosphatase (2.4%) and vomiting (2%).

Tabulated list of adverse reactions

Adverse reactions reported in LUMYKRAS clinical studies are displayed in table 3 below. Frequency categories are defined as follows: 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), and not known (cannot be estimated from available data). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

The safety of LUMYKRAS was evaluated in 740 patients with *KRAS G12C*-mutated solid tumours who received 960 mg orally once daily as monotherapy. The median duration of exposure to LUMYKRAS was 4.2 months (range: 0 to 41).

Table 3. Adverse reactions

MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**
Blood and lymphatic system disorders	Anaemia		
Nervous system disorders		Headache	
Respiratory, thoracic and mediastinal disorders	Cough Dyspnoea	ILD/pneumonitis	
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Constipation Abdominal pain[a]		
Hepatobiliary disorders		Drug-induced liver injury	Hepatitis
Renal and urinary disorders			Renal impairment Renal failure Chronic kidney disease Acute kidney injury
Musculoskeletal and connective tissue disorders	Arthralgia Back pain		
General disorders and administration site conditions	Fatigue	Pyrexia	
Investigations	Aspartate aminotransferase increased Alanine aminotransferase increased	Blood alkaline phosphatase increased Blood bilirubin increased Gamma-glutamyltransferase increased	
Metabolism and nutrition disorders	Decreased appetite	Hypokalaemia	

[a] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower

Description of selected adverse reactions

Elevated liver enzymes
In clinical studies, transient elevations of serum transaminases were observed (see section 4.4). Among 740 patients who received LUMYKRAS 960 mg once daily as monotherapy, elevations of ALT occurred in 12.8% of patients and elevations of AST in 13.1% of patients, with a median time to onset of 6 weeks (range: 1 to 103) and 6 weeks (range: 0 to 42), respectively. Elevations of ALT resulted in dose interruption and/or reduction in 5.9% of patients, and elevations of AST resulted in dose interruption and/or reduction in 5.7% of patients. Elevated bilirubin occurred in 3.2% of patients and resulted in dose interruption and/or reduction in 0.9% of patients.

ILD/pneumonitis
In clinical studies, among 740 patients who received LUMYKRAS 960 mg once daily as monotherapy, ILD/pneumonitis occurred in 1.9% of patients; ILD/pneumonitis was grade 3 or 4 at onset on 0.8% of patients. A case of fatal ILD occurred in a patient with metastatic NSCLC stage IVB treated with LUMYKRAS in a clinical trial. The patient developed lower respiratory tract infection with a fatal outcome despite steroids and antibiotics treatment. The fatal ILD occurred in a setting of massive disease progression. The median time to first onset for ILD/pneumonitis was 10.6 weeks (range: 2 to 43.3 weeks). LUMYKRAS was discontinued due to ILD/pneumonitis in 0.9% of patients (see sections 4.2 and 4.4).

Elderly
In clinical studies, no overall differences in safety or efficacy were observed between elderly patients (≥ 65 years old) and younger patients (see sections 4.2 and 5.2).

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 the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. There is no specific antidote for overdose with LUMYKRAS.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, ATC code: L01XX73

Mechanism of action

Sotorasib is a selective $KRAS^{G12C}$ (Kirsten rat sarcoma viral oncogene homologue) inhibitor, which covalently and irreversibly binds to the unique cysteine of $KRAS^{G12C}$. Inactivation of $KRAS^{G12C}$ by sotorasib blocks tumour cell signalling and survival, inhibits cell growth, and promotes apoptosis selectively in tumours harbouring $KRAS^{G12C}$, an oncogenic driver of tumourigenesis.

Clinical efficacy and safety

LUMYKRAS for the treatment of patients with previously treated KRAS G12C-mutated NSCLC

CodeBreaK 100 phase 2 part A
The efficacy of LUMYKRAS was studied in a single-arm, open-label, multicentre trial (CodeBreaK 100 phase 2 part A) that enrolled patients with locally advanced or metastatic *KRAS G12C*-mutated NSCLC who had disease progression after receiving prior therapy. Key eligibility criteria included progression on an immune checkpoint inhibitor and/or platinum-based chemotherapy and after targeted therapy if actionable oncogenic driver mutations were identified, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumours (RECIST v1.1). All patients were required to have *KRAS G12C*-mutated NSCLC prospectively identified in tumour samples using a validated test (Qiagen therascreen® KRAS RGQ PCR Kit) performed in a central laboratory. Patients with renal impairment, hepatic impairment and active brain metastases were excluded.

A total of 126 patients were enrolled and treated with LUMYKRAS 960 mg once daily as monotherapy until disease progression or unacceptable toxicity; 124 patients had at least one measurable lesion at baseline as assessed by Blinded Independent Central Review (BICR) according to RECIST v1.1 and were included in the analysis for response-related efficacy outcomes. The median duration of treatment was 5.5 months (range: 0 to 15) with 48% of patients treated for ≥ 6 months and 33% of patients treated for ≥ 9 months.

The major efficacy outcome measure was objective response rate (ORR) defined as the proportion of patients who achieved CR or PR as evaluated by a BICR according to RECIST v1.1. Additional efficacy outcome measures included duration of response (DOR), disease control rate (DCR) defined as the proportion of patients who achieved CR, PR and stable disease, time to response (TTR), progression-free survival (PFS), and overall survival (OS).

The baseline demographic and disease characteristics of the study population were: median age 64 years (range: 37 to 80); 50% Female; 82% White, 15% Asian, 2% Black; 70% ECOG PS 1; 96% had stage IV disease; 99% with non-squamous histology; 81% former smokers, 12% current smokers, 5% never smokers.

All patients received at least 1 prior line of systemic therapy for metastatic NSCLC; 43% received only 1 prior line of therapy, 35% received 2 prior lines of therapy, 22% received 3 prior lines of therapy, 91% received prior anti-PD-1/PD-L1 immunotherapy, 90% received prior platinum-based chemotherapy, 81% received both platinum-based chemotherapy and anti-PD-1/PD-L1. The sites of known extra-thoracic metastasis included 48% bone, 21% brain, and 21% liver.

Efficacy results are summarised in table 4.

Table 4. Efficacy results in CodeBreaK 100 for patients with *KRAS G12C*-mutated NSCLC (CodeBreaK 100 phase 2 part A)

Efficacy parameters	**LUMYKRAS N = 124**
ORR, % (95% CI)[a,c]	37.1 (28.6, 46.2)
Complete response (CR), %	2.4
Partial response (PR), %	34.7
DOR[a,d]	
Number of responders	46
Median[b], months (range)	11.1 (6.9, 15.0)
Censored, %	39.0
Patients with duration ≥ 6 months, %	63.0

CI = confidence interval; DOR = duration of response; ORR = objective response rate
[a] Response-related efficacy outcome
[b] Estimated using Kaplan-Meier method
[c] Based on 01 December 2020 data cut
[d] Based on 20 June 2021 data cut

Paediatric population

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

Conditional marketing authorisation

This medicinal product has been authorised under a so-called '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

Absorption

Bioavailability of sotorasib has not been investigated in humans. Following an oral, single dose administration, sotorasib was absorbed with median time to achieve peak concentration of 1-2 hours.

In a dose comparison sub-study (CodeBreaK 100 phase 2 part B) in patients receiving sotorasib 240 mg or 960 mg once daily, after 8 daily doses, C_{max} and $AUC_{0\text{-}24\ hour}$ for 240 mg were both 22% lower than 960 mg.

Effect of food
Following administration of sotorasib with a high-fat, high-calorie meal, there was no effect on C_{max}, and AUC increased by 38% compared to administration under fasted conditions. Sotorasib can be administered with or without food.

Distribution

The geometric mean apparent volume of distribution after 960 mg PO QD for 8 consecutive days of sotorasib was 211 L (determined using noncompartmental analysis). *In vivo*, plasma protein binding of sotorasib was 97.6% and sotorasib bound preferentially to alpha-1-acid glycoprotein *in vitro*.

Biotransformation

The main metabolic pathways of sotorasib were non-enzymatic conjugation and oxidative metabolism. *In vitro* data indicate that sotorasib is metabolised by cytochrome P4502C8, CYP3A4, and CYP3A5, and is a substrate of P-glycoprotein (P-gp). Following single oral administration of a radioactive sotorasib dose of 720 mg, a cysteine adduct (formed through hydrolysis of a glutathione adduct) and an oxidative metabolite resulting from CYP3A-mediated cleavage of the piperazine acrylamide moiety were the primary circulating metabolites. Neither of these metabolites were pharmacologically active.

Elimination

The geometric mean apparent clearance after 960 mg orally once daily for 8 consecutive days of sotorasib was 26.2 L/hour (determined using noncompartmental analysis). The mean half-life is 5 hours. Steady state was reached within 22 days and remained stable. Sotorasib is primarily eliminated in faeces, with approximately 74% of the dose recovered in faeces and 6% (1% unchanged) recovered in urine.

Linearity/non-linearity

Sotorasib exhibited nonlinear pharmacokinetics over a range of single and multiple oral administration doses studied between 180 to 960 mg once daily as C_{max} and $AUC_{0\text{-}24\ hour}$ were less than dose

proportional. The average C_{max} and $AUC_{0\text{-}24\ hour}$ values following multiple doses were similar for all dosing regimens from 180 mg orally once daily to 960 mg orally once daily. Exposure to sotorasib decreases over time following 960 mg orally once daily dosing regimen until steady state is reached. Steady state plasma concentrations were achieved by approximately 3 weeks across the phase 1 and phase 2 clinical studies across all sotorasib doses.

Pharmacokinetics in special populations

Initial results of a population PK analysis suggests no clinically meaningful differences in the pharmacokinetics of sotorasib based on age, sex, race or ethnicity, body weight, line of therapy, ECOG PS, serum albumin, mild renal impairment (CrCL ≥ 60 mL/min), or mild hepatic impairment (AST or ALT < 2.5 × ULN or total bilirubin < 1.5 × ULN). The effect of moderate to severe renal impairment on sotorasib pharmacokinetics has not been studied.

Hepatic impairment

Compared to subjects with normal hepatic function after a 960 mg LUMYKRAS administration, the mean systemic exposure AUC_{inf} of sotorasib decreased by 25.4% in subjects with moderate impairment (Child-Pugh B) and increased by 3.6% in subjects with severe hepatic impairment (Child-Pugh C). The unbound AUC_{inf} of sotorasib increased by 1.8-fold in subjects with moderate hepatic impairment and by 6-fold in patients with severe hepatic impairment.

5.3 Preclinical safety data

Mutagenicity

Sotorasib was not mutagenic in a bacterial mutagenicity (Ames) assay. Sotorasib was not genotoxic in the *in vivo* rat micronucleus and comet assays.

Carcinogenicity

Carcinogenicity studies have not been performed with sotorasib.

Reproductive toxicity

In rat and rabbit embryo-foetal development studies, oral sotorasib was not teratogenic.

In the rat, there were no effects on embryo-foetal development up to the highest dose tested (3.9 times higher than the exposure at the maximum recommended human dose [MRHD] of 960 mg based on area under the curve [AUC]).

In the rabbit, lower foetal body weights and a reduction in the number of ossified metacarpals in foetuses were observed only at the highest dose level tested (2.2 times higher than the exposure at the MRHD of 960 mg based on AUC), which was associated with maternal effects such as decreased body weight gain and food consumption during the dosing phase. Reduced ossification, as evidence of growth retardation associated with reduced foetal body weight, was interpreted as a non-specific effect in the presence of significant maternal toxicity.

Impairment of fertility

Fertility/early embryonic development studies were not conducted with sotorasib. There were no adverse effects on male or female reproductive organs in general toxicology studies conducted in dogs and rats.

Other nonclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

- Renal toxicity observed in repeat-dose toxicity studies in rats.

Environmental risk assessment

Environmental risk assessment studies have shown that sotorasib has the potential to be very persistent to the environment (see section 6.6). There is no potential for bioaccumulation or toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Cellulose, microcrystalline (E460(i))
Lactose monohydrate
Croscarmellose sodium (E468)
Magnesium stearate (E470b)

Film-coating

Poly(vinyl alcohol) (E1203)
Titanium dioxide (E171)
Macrogol 4000 (E1521)
Talc (E553b)
Iron oxide yellow (E172)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be dispersed with other liquids than that mentioned in section 4.2. Acidic beverages (e.g. fruit juices) should also be excluded.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

LUMYKRAS 120 mg film-coated tablets

PVC/PE/PVDC blisters with aluminium foil backing containing 8 film-coated tablets. Pack sizes of 240 film-coated tablets (1 carton with 30 blisters) and multipack with 720 (3 × 240) film-coated tablets.

HDPE bottle with a child-resistant polypropylene cap and aluminium foil induction seal liner containing 120 film-coated tablets. Pack size of 240 film-coated tablets (1 carton with 2 bottles).

LUMYKRAS 240 mg film-coated tablets

PVC/PCTFE perforated unit dose blisters with aluminium foil backing containing 8 film-coated tablets. Pack size of 120 film-coated tablets (1 carton with 15 blisters).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.,
Minervum 7061,
4817 ZK Breda,
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1603/001
EU/1/21/1603/002
EU/1/21/1603/003
EU/1/21/1603/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 06 January 2022
Date of latest renewal: 20 November 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://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

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

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Amgen Europe B.V.,
Minervum 7061,
4817 ZK Breda,
The Netherlands

Amgen NV,
Telecomlaan 5-7,
1831 Diegem,
Belgium

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 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.

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 confirm the efficacy and safety of sotorasib in the treatment of patients with *KRAS G12C*-mutated NSCLC, the MAH should submit the clinical study report for the analysis of the phase 3 CodeBreaK 202 study (study 20190341) comparing sotorasib in combination with Platinum Doublet versus pembrolizumab Platinum Doublet combination for the treatment of PD-L1 Negative *KRAS G12C* Positive Advanced/Metastatic NSCLC.	Primary analysis clinical study report (CSR) Q2 2026 Final analysis CSR Q2 2028

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARTON (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

LUMYKRAS 120 mg film-coated tablets
sotorasib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 120 mg sotorasib.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

240 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.
Do not chew, crush or split the tablet.

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

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

Amgen Europe B.V.,
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1603/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

LUMYKRAS 120 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK BLISTER (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

LUMYKRAS 120 mg film-coated tablets
sotorasib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 120 mg sotorasib.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
Multipack: 720 (3 packs of 240) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.
Do not chew, crush or split the tablet.

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

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

Amgen Europe B.V.,
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1603/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

LUMYKRAS 120 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON OF MULTIPACK BLISTER (without blue box)

1. NAME OF THE MEDICINAL PRODUCT

LUMYKRAS 120 mg film-coated tablets
sotorasib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 120 mg sotorasib.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
240 film-coated tablets. Component of a multipack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.
Do not chew, crush or split the tablet.

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

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

Amgen Europe B.V.,
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1603/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

LUMYKRAS 120 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

LUMYKRAS 120 mg tablet
sotorasib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

LUMYKRAS 120 mg film-coated tablets
sotorasib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 120 mg sotorasib.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
240 (2 bottles of 120) film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.
Do not chew, crush or split the tablet.

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

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

Amgen Europe B.V.,
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1603/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

LUMYKRAS 120 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

LUMYKRAS 120 mg film-coated tablets
sotorasib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 120 mg sotorasib.

3. LIST OF EXCIPIENTS

Lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
120 film-coated tablets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.
Do not chew, crush or split the tablet.

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

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

Amgen Europe B.V.,
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1603/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BLISTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

LUMYKRAS 240 mg film-coated tablets
sotorasib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 240 mg sotorasib.

3. LIST OF EXCIPIENTS

Lactose monohydrate. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

120 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.
Do not chew, crush or split the tablet.

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

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

Amgen Europe B.V.,
Minervum 7061,
4817 ZK Breda,
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1603/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

LUMYKRAS 240 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

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

LUMYKRAS 240 mg tablet
sotorasib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Amgen Europe B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

LUMYKRAS 120 mg film-coated tablets
LUMYKRAS 240 mg film-coated tablets
sotorasib

▼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 LUMYKRAS is and what it is used for

LUMYKRAS contains the active substance sotorasib and belongs to a group of medicines known as antineoplastic agents (cancer medicines).

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

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

How does LUMYKRAS work?

The abnormal *KRAS G12C* protein, acts to help make cancer cells grow out of control. LUMYKRAS attaches to the protein and stops it from working, which may slow down or stop the growth of the cancer.

If you have any questions about how LUMYKRAS 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 LUMYKRAS

Do not take LUMYKRAS

- if you are allergic to sotorasib 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 LUMYKRAS.

Tell your doctor, pharmacist or nurse if you have a history of liver problems. Your doctor may carry out blood tests to check your liver function, and may decide to either reduce the dose of LUMYKRAS or stop your treatment.

Tell your doctor if you have ever had any other lung problems. Some lung problems may get worse during treatment with LUMYKRAS, as LUMYKRAS may cause inflammation of the lungs during treatment. Symptoms may be similar to those from lung cancer. Tell your doctor right away if you have any new or worsening symptoms including difficulty in breathing, shortness of breath, or cough with or without mucous, or fever.

Children and adolescents

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

Other medicines and LUMYKRAS

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, vitamins and herbal supplements. This is because LUMYKRAS can affect the way some other medicines work, and some other medicines can affect the way LUMYKRAS works.

The following medicines may reduce how well LUMYKRAS works:
- Medicines used to reduce stomach acid and to treat stomach ulcers, indigestion and heartburn (see section 3) such as:
  - dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole sodium, or rabeprazole (medicines known as ‘proton pump inhibitors’)
  - ranitidine, famotidine, cimetidine (medicines known as ‘H_2 receptor antagonists’)
- Rifampicin (used to treat tuberculosis)
- Medicines used to treat epilepsy called phenytoin, phenobarbital or carbamazepine (also used to treat nerve pain)
- St. John’s wort (herbal medicine used to treat depression)
- Enzalutamide (used to treat prostate cancer)

LUMYKRAS may reduce how well the following medicines work:
- Medicines used to treat severe pain, such as alfentanil or fentanyl
- Medicines used in organ transplantation to prevent organ rejection, such as cyclosporine, sirolimus, everolimus or tacrolimus
- Medicines used to reduce high blood pressure, such as amlodipine and manidipine
- Medicines used to reduce cholesterol levels, such as simvastatin, atorvastatin, or lovastatin
- Midazolam (used to treat acute seizures or as a sedative before or during surgery or medical procedures)
- Medicines used to treat heart rhythm problems, such as dronedarone or amiodarone
- Medicines known as anticoagulants that stop your blood clotting, such as rivaroxaban or apixaban

LUMYKRAS may increase the risk for side effects with the following medicines:
- Medicines used to treat certain cancers or inflammatory conditions, such as methotrexate, mitoxantrone, topotecan or lapatinib
- Medicines used to treat heart failure, such as digoxin
- Medicines used to lower cholesterol, such as rosuvastatin

Contraception

If you take LUMYKRAS whilst using oral contraceptives, the oral contraceptives may be ineffective. In addition, you should use another reliable method of birth control such as a barrier method (e.g. condom) so you do not become pregnant while you are taking this medicine. Talk to your doctor about the right methods of contraception for you and your partner.

Pregnancy, breast-feeding and fertility

Pregnancy

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

You should not become pregnant while taking this medicine because the effects of LUMYKRAS in pregnant women are not known, it could harm the baby. If you are able to become pregnant, you must use highly effective contraception while on treatment and for at least 7 days after stopping treatment.

Breast-feeding

Do not breast-feed while taking this medicine and for 7 days after the last dose. This is because it is not known whether the ingredients in LUMYKRAS pass into breast milk and could therefore harm your baby.

Driving and using machines

LUMYKRAS has no marked influence on the ability to drive and use machines.

LUMYKRAS contains lactose

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

LUMYKRAS contains sodium

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

3. How to take LUMYKRAS

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 change your dose or stop taking LUMYKRAS unless your doctor or pharmacist tells you to. Your doctor or pharmacist may decrease the dose or stop your medicine depending on how well you tolerate it.
- The recommended dose is 960 mg (eight 120 mg tablets or four 240 mg tablets) once a day. Take your daily dose of LUMYKRAS by mouth once a day, at the same time each day.
- LUMYKRAS can be taken with or without food.

- Swallow the tablets whole. You can disperse the tablets in water but do not chew, crush, or split the tablets.
- If you cannot swallow LUMYKRAS tablets whole:
  - Place your daily dose of LUMYKRAS in half a glass (not less than 120 mL) of plain, 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 tablets are in small pieces (the tablets will not dissolve completely). The appearance of the mixture may range from pale to bright yellow.
  - Drink the mixture right away.
  - Rinse the glass with an additional half a glass of water and drink right away to make sure that you have taken the full dose of LUMYKRAS.
  - If you do not drink all of the mixture immediately, stir the mixture again before you finish drinking it. Drink all of the mixture within two hours of preparation.
- If necessary, your doctor may recommend you receive LUMYKRAS through a feeding tube.

If you need to take a medicine to reduce stomach acid such as a proton pump inhibitor or an H_2 receptor antagonist, take LUMYKRAS with an acidic beverage (such as cola). Alternatively, you may use a local antacid (such as magnesium hydroxide or calcium carbonate) and, in that case, LUMYKRAS should be taken either 4 hours before or 10 hours after that medicine (see section 2).

If you take more LUMYKRAS than you should

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

If you vomit after taking LUMYKRAS

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

If you forget to take LUMYKRAS

If you forget to take a dose of LUMYKRAS at your regular scheduled time, and less than 6 hours have passed, take your dose as normal. If more than 6 hours have passed from your regular scheduled time, do not take the dose. Take your next dose at your regular scheduled time the next day.

4. Possible side effects

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

Very common and serious possible side effects of LUMYKRAS are increased blood levels of certain liver enzymes (AST/ALT), which are a sign of liver problems. Your doctor may do blood tests to check how well your liver is working and may decide to either reduce the dose of LUMYKRAS or stop your treatment (see section 2).

Other possible side effects of LUMYKRAS may include:

Very common (may affect more than 1 in 10 people)
- Diarrhoea
- Feeling sick (nausea)
- Feeling tired
- Vomiting
- Constipation
- Stomach pain
- Joint pain
- Back pain

- Shortness of breath
- Cough
- Low red blood cell count (anaemia) which may cause tiredness and fatigue
- Decreased appetite

Common (may affect up to 1 in 10 people)
- Headache
- Fever
- High levels of some enzymes including blood enzymes seen in tests (increased alkaline phosphatase, bilirubin and gamma-glutamyltransferase)
- Liver injury
- Inflammation of the lungs called “interstitial lung disease”
- Changes to blood tests (decreased blood levels of potassium)

Uncommon (may affect up to 1 in 100 people)
- Kidney problems, including kidney failure
- Inflammation of the liver (hepatitis)

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 LUMYKRAS

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 blister after EXP. The expiry date refers to the last day of that month.

Do not use this medicine after the expiry date which is stated on the carton and bottle after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

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 LUMYKRAS contains

- The active substance is sotorasib. Each film-coated tablet contains 120 mg or 240 mg of sotorasib.
- The other ingredients are:
  - Cellulose, microcrystalline (E460(i))
  - Lactose monohydrate
  - Croscarmellose sodium (E468)
  - Magnesium stearate (E470b)
- The tablets are coated with:
  - Poly(vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 4000 (E1521), talc (E553b), and iron oxide yellow (E172)

See LUMYKRAS contains lactose and LUMYKRAS contains sodium in section 2.

What LUMYKRAS looks like and contents of the pack

LUMYKRAS 120 mg film-coated tablets

Each film-coated tablet is supplied as a yellow, oblong-shaped, film-coated tablet, with “AMG” on one side and “120” on the other side.

- LUMYKRAS is provided in blisters containing 8 film-coated tablets in packs sizes of 240 film-coated tablets (1 carton with 30 blisters) and multipack with 720 (3 × 240) film-coated tablets.
- LUMYKRAS is provided in bottles containing 120 film-coated tablets in a pack size of 240 film-coated tablets (1 carton with 2 bottles).

LUMYKRAS 240 mg film-coated tablets

Each film-coated tablet is supplied as a yellow, oval-shaped, film-coated tablet, with “AMG” on one side and “240” on the other side.

- LUMYKRAS is provided in perforated unit dose blisters containing 8 film-coated tablets in pack sizes of 120 film-coated tablets (1 carton with 15 blisters).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
Amgen Europe B.V.,
Minervum 7061,
4817 ZK Breda,
The Netherlands

Marketing Authorisation Holder
Amgen Europe B.V.,
Minervum 7061,
4817 ZK Breda,
The Netherlands

Manufacturer
Amgen NV,
Telecomlaan 5-7,
1831 Diegem,
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
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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 web site: https://www.ema.europa.eu.

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