SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

LUMYKRAS 240 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

LUMYKRAS 240 mg film-coated tablets

Each film-coated tablet contains 240 mg of sotorasib.

Excipient with known effect

Each film-coated tablet contains 52.5 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

LUMYKRAS 240 mg film-coated tablets

Yellow, immediate release, 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 is indicated as monotherapy for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have progressed on, or are intolerant to, platinum-based chemotherapy and/or anti PD-1/PD-L1 immunotherapy.

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 of LUMYKRAS is 960 mg (four 240 mg tablets) orally once daily, at the same time each day, with or without food.

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

Missed doses
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. Additional doses should not be taken in place of a missed dose.
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. Dose reduction levels are summarised in table 1. Dose modifications for adverse reactions are provided in table 2.

If toxicity events occur, a maximum of two dose reductions are permitted. LUMYKRAS must be discontinued if 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 (four 240 mg tablets) once daily
First dose reduction	480 mg (two 240 mg tablets) once daily
Second dose reduction	240 mg (one 240 mg tablet) once daily

Table 2. Recommended dose modifications for sotorasib

Adverse reaction	**Severity**[a]	**Dose modification**
Hepatotoxicity	Grade 2 AST or ALT with symptoms or Grade ≥ 3 AST or ALT	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN, in the absence of alternative causes	• Permanently discontinue treatment
Interstitial Lung	Any Grade	• Stop treatment if

Adverse reaction	Severity[a]	Dose modification
Disease/(ILD)/pneumonitis		ILD/pneumonitis is suspected • Permanently discontinue if ILD/pneumonitis is confirmed
Nausea or vomiting despite appropriate supportive care (including anti-emetic therapy)	Grade 3 to 4	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level
Diarrhoea despite appropriate supportive care (including anti-diarrhoeal therapy)	Grade 3 to 4	• Stop treatment until recovered to ≤ grade 1 or to baseline grade • After recovery, resume treatment at the next dose reduction level
Other adverse reactions	Grade 3 to 4	• 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

Special populations

Elderly
In clinical studies, no overall differences in safety or efficacy were observed between elderly patients (≥ 65 years old) and younger patients. No dose adjustment is recommended in elderly patients (see section 5.2).

Hepatic impairment
No dose adjustment is recommended for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment (see section 5.2). Dose adjustment should be considered in patients with severe hepatic impairment (Child-Pugh C). There are no data on the clinical safety and efficacy of multiple doses of LUMYKRAS when administered to patients with severe hepatic impairment (Child-Pugh C). LUMYKRAS should be used with caution in patients with severe hepatic impairment.

Renal impairment
Based on population pharmacokinetic analysis, 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) (see section 5.2).

Paediatric population
The safety and efficacy of LUMYKRAS in children and adolescents aged less than 18 years have not been established. No data are available.

Method of administration

LUMYKRAS is for oral use. The tablets should normally be swallowed whole, unless the patient has difficulty swallowing solids, in which case the following instruction should be followed.

Administration to patients who have difficulty swallowing solids
Patients should disperse tablets in 120 mL of non-carbonated, room-temperature water without crushing. Other liquids must not be used. Patients should stir until the tablets are dispersed into small pieces (the tablet will not completely dissolve) 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 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

LUMYKRAS can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis. Sotorasib has been associated with transient elevations of serum transaminases (ALT and AST) (see section 4.8). These elevations improved or resolved with dose modification or permanent discontinuation of treatment and did not result in any cases of liver failure or fatal cases in clinical studies. Cases of liver enzyme increase can be asymptomatic. Liver function tests (ALT, AST, and total bilirubin) must be monitored 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 who develop transaminase and/or bilirubin elevations. Based on the severity of the laboratory abnormalities, treatment with LUMYKRAS must be stopped until recovered to ≤ grade 1 or to baseline grade, and the dose must either be modified or permanently discontinue treatment as recommended (see section 4.2).

Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis occurred in patients treated with LUMYKRAS with prior exposure to immunotherapy or radiotherapy (see section 4.8). 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 potential causes of ILD/pneumonitis are identified (see section 4.2)

Lactose intolerance

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

This medicine 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

Effects of other medicinal products on sotorasib

Acid-reducing agents
Co-administration of sotorasib with a PPI (omeprazole) or an H2 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 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.

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 with LUMYKRAS is not recommended because the impact on sotorasib efficacy is unknown.

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. If co-administration cannot be avoided, adjust the CYP3A4 substrate dosage in accordance with the current summary of product characteristics.

Transporter systems
P-glycoprotein (P-gp) Substrates
Coadministration of LUMYKRAS with digoxin (a P-gp substrate) increased digoxin Cmax by 91% and AUC by 21%.

Avoid coadministration of LUMYKRAS with P-gp substrates, for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the P-gp substrate dosage in accordance with its Prescribing Information.

Breast Cancer Resistance Protein (BCRP) substrates
Sotorasib is a weak BCRP inhibitor. Co-administration of sotorasib with a BCRP substrate led to an increase in the plasma concentrations of the BCRP substrate, which may increase the effects of these substrates.

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

When co-administered with LUMYKRAS, monitor for adverse reactions of the BCRP substrate and decrease the BCRP substrate dosage in accordance with the current summary of product characteristics.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of sotorasib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). 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 newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from LUMYKRAS therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

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

The safety of LUMYKRAS was evaluated in 359 patients with *KRAS G12C*-mutated solid tumours who received 960 mg orally once daily as monotherapy. The median duration of exposure to LUMYKRAS was 4.1 months (range: 0.02 to 21).

The most common adverse reactions were diarrhoea (34%), musculoskeletal pain (31%), nausea (25%), fatigue (21%), hepatotoxicity (19%) and cough (16%). The most common severe (grade ≥ 3) adverse reactions were increased ALT (5%), increased AST (4%), and diarrhoea (4%). The most common adverse reactions leading to permanent discontinuation of treatment were increased ALT (1%), increased AST (1%) and drug-induced liver injury (1%). The most common adverse reactions leading to dose modification were increased ALT (6%), increased AST (6%), and diarrhoea (6%).

The most common laboratory abnormalities (≥ 25%) were decreased lymphocytes, decreased haemoglobin, increased AST, decreased calcium, increased urine protein, increased ALT, increased alkaline phosphatase, and decreased sodium.

Tabulated list of adverse reactions

Adverse reactions reported in LUMYKRAS clinical studies are displayed in table 3 below. Frequency is provided by MedDRA category: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 and < 1/1,000), very rare (< 10,000). Within each system organ class, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions

MedDRA system organ class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to < 1/10)**
Blood and lymphatic system disorders	Anaemia	

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)
Nervous system disorders	Headache	
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough[a]	
Cardiovascular disorders		Hypertension
Gastrointestinal disorders	Diarrhoea Nausea Vomiting Abdominal pain[b] Constipation	
Hepatobiliary Disorders	Hepatotoxicity[c]	
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[d]	
General disorders and administration site conditions	Fatigue Pyrexia	Peripheral oedema
Metabolism and nutrition disorders		Decreased appetite Hypokalaemia Hyponatraemia Hypocalcaemia
Infections		Pneumonia Urinary tract infection
Skin and subcutaneous tissue disorders		Rash
Investigations		Blood alkaline phosphatase increased

[a] Cough includes cough, productive cough, and upper-airway cough syndrome.

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

[c] Hepatotoxicity includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatitis, hepatotoxicity, liver function test increased, and transaminases increased.

[d]Musculoskeletal pain includes arthralgia, myalgia and back pain

Description of selected adverse reactions

Hepatotoxicty

Among 359 patients who received LUMYKRAS in CodeBreaK 100, a total of 17% of patients who received LUMYKRAS had increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST); 6% were Grade 3 and 0.6% were Grade 4. The median time to first onset of increased ALT/AST was 8 weeks (range: 0.3 to 42). Increased ALT/AST leading to dose interruption or reduction occurred in 7% of patients. LUMYKRAS was discontinued due to increased ALT/AST in 1.7% of patients. In addition to dose interruption or reduction, 5% of patients received corticosteroids for the treatment of hepatotoxicity.

Interstitial Lung Disease (ILD)/Pneumonitis

Among 359 patients who received LUMYKRAS in CodeBreaK 100, ILD/pneumonitis occurred in 0.8% of patients, all cases were Grade 3 or 4 at onset. The median time to first onset for ILD/pneumonitis was 2 weeks (range: 2 to 18 weeks). LUMYKRAS was discontinued due to ILD/pneumonitis in 0.6% of patients.

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:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no clinical experience with overdose with sotorasib. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, ATC code: L01XX73

Mechanism of action

Sotorasib is a potent and highly selective $KRAS^{G12C}$ (Kirsten rat sarcoma viral oncogene homolog) 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 across multiple cancer types. The potency and selectivity of sotorasib is enhanced through the unique binding to both the P2 pocket and the His95 surface groove, locking the protein in an inactive state that prevents downstream signalling, without affecting wild-type KRAS.

Sotorasib demonstrated *in vitro* and *in vivo* inhibition of $KRAS^{G12C}$ with minimal detectable off-target activity against other cellular proteins and processes. Sotorasib impaired oncogenic signalling and tumour cell survival at clinically relevant exposures in numerous pre-clinical models expressing $KRAS^{G12C}$. Sotorasib also enhanced antigen presentation and inflammatory cytokine production only in tumour cells with $KRAS^{G12C}$. Sotorasib induced anti-tumour inflammatory responses and immunity, driving permanent and complete tumour regressions in immunocompetent mice implanted with $KRAS^{G12C}$ expressing tumours.

Clinical efficacy and safety

LUMYKRAS for the treatment of previously treated KRAS G12C-mutated NSCLC (CodeBreaK 100)
The efficacy of LUMYKRAS was demonstrated in a single-arm, open-label, multicentre trial (CodeBreaK 100) 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, 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 performed in a central laboratory.

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 measures were objective response rate (ORR) and duration of response (DOR) as evaluated by a BICR according to RECIST v1.1. Additional efficacy outcome measures included disease control rate (DCR), 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. The ORR was 37% (95% CI: 29, 47). The patients with objective responses had DOR ranging from 1.2 to 11.1 months, and 43% were still on therapy with ongoing response after a median duration of follow-up of 9.6 months. The median TTR was 1.4 months (range: 1.2 to 10.1), with 70% of responses occurring within the first 7 weeks.

Table 4. Efficacy results in CodeBreaK 100 for patients with KRAS G12C-mutated NSCLC

Efficacy parameter	**LUMYKRAS N = 124**
ORR, % (95% CI)[a]	37.1 (28.6, 46.2)
Complete response (CR), %	2.4
Partial response (PR), %	34.7
DOR[a]	
Median[b], months (range)	10.0 (1.2, 11.1)
Patients with duration ≥ 6 months, %	56.5
DCR (95% CI)	80.6 (72.6, 87.2)
PFS[a]	
Median, months (95% CI)	6.8 (5.1, 8.2)
6-month PFS, % (95% CI)	52.2 (42.6, 60.9)
9-month PFS, % (95% CI)	37.2 (28.1, 46.3)
Efficacy parameter	**LUMYKRAS N = 126**
OS	
Median, months (95% CI)	12.5 (10.0, NE)
6-month OS, % (95% CI)	75.5 (66.8, 82.2)
9-month OS, % (95% CI)	63.5 (54.3, 71.4)
12-month OS, % (95% CI)	51.4 (41.9, 60.1)

CI = confidence interval; DCR = disease control rate; DOR = duration of response; NE = not estimable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival

[a] Response-related efficacy outcome

[b] Estimated using Kaplan-Meier method

Cardiac electrophysiology
The effect of sotorasib on the QT interval was assessed in 156 patients administered sotorasib 960 mg once daily in clinical studies. Sotorasib did not prolong the QT interval to any clinically relevant extent. At peak concentrations, the mean change from baseline was less than 5 msec. No patients had a large mean increase in QTc (> 20 msec) in the study.

Paediatric population

The Medicines and Healthcare products Regulatory 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).

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 Medicines and Healthcare products Regulatory 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

Following an oral, single-dose administration, sotorasib was absorbed with median time to achieve peak concentration of 1 hour.

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 mean volume of distribution at steady state of sotorasib was 211 L. *In vitro*, plasma protein binding of sotorasib was 89%.

Biotransformation

The main metabolic pathways of sotorasib were conjugation and oxidative metabolism.

Elimination

At 960 mg once daily, the steady state apparent clearance is 26.2 L/hr. The mean half-life is 5 hours. Steady state was reached within 22 days and remained stable. No accumulation with multiple dosing was observed. Sotorasib is primarily eliminated in faeces, with approximately 74% of the dose recovered in faeces and 6% (1% unchanged) recovered in urine.

Pharmacokinetics in special populations

No clinically meaningful differences in the pharmacokinetics of sotorasib were observed based on age, sex, race or ethnicity, body weight, line of therapy, ECOG PS or mild renal impairment (CrCL: ≥ 60 mL/min). The effect of moderate to severe renal impairment on sotorasib pharmacokinetics has not been studied.

Hepatic Impairment
Compared to subjects with normal liver function, AUC_{inf} of sotorasib was decreased by 25.4% in subjects with moderate impairment and increased by 3.6% in subjects with severe impairment. The unbound AUC_{inf} of sotorasib increased by 1.8-fold in subjects with moderate hepatic impairment and by 6.3-fold in subject 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.

General toxicology

In rats, renal toxicity including minimal to marked histologic tubular degeneration/necrosis and increased kidney weight, urea nitrogen, creatinine, and urinary biomarkers of renal tubular injury were present at doses resulting in exposures approximately ≥ 0.5 times the human AUC at the clinical dose of 960 mg. Increases in cysteine S-conjugate β-lyase pathway metabolism in the rat kidney compared to human may make rats more susceptible to renal toxicity than humans due to local formation of a putative sulphur-containing metabolite..

In the 3-month toxicology study in dogs, sotorasib induced findings in the liver (centrilobular hepatocellular hypertrophy), pituitary gland (hypertrophy of basophils), and thyroid gland (marked follicular cell atrophy, moderate to marked colloid depletion, and follicular cell hypertrophy) at exposures approximately 0.4 times the human exposure based on AUC at the clinical dose of 960 mg. These findings may be due to an adaptive response to hepatocellular enzyme induction and subsequent reduced thyroid hormone levels (i.e. secondary hypothyroidism).

Environmental risk assessment

Environmental risk assessment studies have shown that sotorasib has the potential to be 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

Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

Film-coating

Polyvinyl alcohol
Titanium dioxide
Polyethylene glycol
Talc
Iron oxide yellow

6.2 Incompatibilities

None

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 240 mg film-coated tablets

PVC/Aclar 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 Limited
216 Cambridge Science Park
Milton Road
Cambridge
CB4 0WA
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 13832/0101

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

18/09/2025

10 DATE OF REVISION OF THE TEXT

18/09/2025