1. NAME OF THE MEDICINAL PRODUCT

LUMYKRAS 120 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 120 mg of sotorasib.

Excipient with known effect
Each film-coated tablet contains 108 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LUMYKRAS is indicated for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an approved test, who have received at least one prior 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) 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. Dose reduction levels are summarized in table 1. Dose modifications for adverse reactions are provided in table 2 (see section 5.2).

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 (eight 120 mg tablets) once daily
First dose reduction	480 mg (four 120 mg tablets) once daily
Second dose reduction	240 mg (two 120 mg tablets) 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 Disease (ILD)/pneumonitis	Any grade	• Stop treatment if ILD/pneumonitis is suspected. • Permanently discontinue treatment if ILD/pneumonitis is confirmed.
Nausea, vomiting, or diarrhea persisting despite supportive care (including anti-emetic or anti-diarrheal 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

Co-administration of LUMYKRAS with acid-reducing agents

Co-administration of proton pump inhibitors (PPIs) or H2 receptor antagonists with LUMYKRAS is not recommended. If treatment with an acid-reducing agent is required a local antacid may be used, LUMYKRAS should be taken either 4 hours before or 10 hours after administration of a local antacid (see section 4.5).

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 (AST or ALT< 2.5 × ULN or total bilirubin < 1.5 × ULN). Administration of sotorasib in subjects with moderate and severe hepatic impairment is not recommended.

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 exercized when treating patients with moderate, severe and end stage renal impairment (see section 5.2).

Pediatric population
The safety and efficacy of LUMYKRAS in children and adolescents under the age of 18 years have not yet been established.

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.

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. dyspnea, 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 metabolized 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 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 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%.

Co-administration of PPIs and H2 receptor antagonists with LUMYKRAS is not recommended because the impact on sotorasib efficacy is unknown. If treatment with an acid-reducing agent is required, LUMYKRAS should be taken 4 hours before or 10 hours after administration of a local antacid (see section 4.2).

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 metabolized 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 fetus 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 diarrhea (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 diarrhea (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 diarrhea (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	Anemia		
Nervous system disorders		Headache	
Respiratory, thoracic and mediastinal disorders	Cough Dyspnea	ILD/pneumonitis	
Gastrointestinal disorders	Diarrhea 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	

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)
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 authorization of the medicinal product is important. It allows continous monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

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
The efficacy of LUMYKRAS was studied 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 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 summarized in table 4.

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

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

Pediatric population

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

Conditional marketing authorization

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.

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 metabolized 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 PO QD 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 QD 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 QD to 960 mg QD. Exposure to sotorasib decreases over time following 960 mg QD 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 or hepatic impairment on sotorasib pharmacokinetics has not been studied.

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-fetal development studies, oral sotorasib was not teratogenic.

In the rat, there were no effects on embryo-fetal 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 fetal body weights and a reduction in the number of ossified metacarpals in fetuses 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 fetal 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, Non-bovine (E470b)

Film-coating

Polyvinyl 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

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. It is recommended to keep the medicine at room temperature.

6.5 Nature and contents of container

PVC/PE/PVDC blisters with aluminum foil backing containing 8 film-coated tablets. Pack sizes of 240 film-coated tablets (1 carton with 30 blisters).

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

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. MANUFACTURER

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

8. LICENSE HOLDER

Amgen Europe B.V.
P.O. BOX 53313
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9 LICENSE NUMBER

169-95-37013

Revised in December 2024