Date: 16 February 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Lumykras

International non-proprietary name: sotorasib

Pharmaceutical form: film-coated tablets

Dosage strength: 120 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Amgen Switzerland AG

Marketing Authorisation No.: 67693

Decision and Decision date: approved (temporary authorisation in accordance with Art. 9a TPA) on 16 December 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ASAT	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCRP	Breast cancer resistance protein
Cmax	Maximum observed plasma/serum concentration of drug
CNS	Central nervous system
CR	Complete response
CYP	Cytochrome P450
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
ERA	Environmental Risk Assessment
GDP	Guanosine diphosphate
GLP	Good Laboratory Practice
hERG	human Ether-a-go-go related gene
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
KRAS	Kirsten rat sarcoma viral oncogene homologue
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MATE1/2K	multidrug and toxin extrusion protein 1/2K
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PD-1	programmed death protein 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
P-gp	Permeability glycoprotein
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
QTcF	QT interval with Fridericia's correction
RECIST	Response evaluation criteria in solid tumours
RMP	Risk Management Plan
SAE	Serious adverse events
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment emergent adverse event
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance sotorasib of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a[decies] no. 2 of the TPA. The Orphan Status was granted on 21 November 2019.

Temporary authorisation for human medical products
The applicant requested a temporary authorisation in accordance with Art. 9a TPA.

2.2 Indication and Dosage

2.2.1 Requested Indication

LUMYKRAS is indicated as monotherapy for the treatment of adult patients with previously treated KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC).

2.2.2 Approved Indication

LUMYKRAS is indicated as monotherapy for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) who have experienced progression after prior treatment with platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy (see "Clinical efficacy").

The efficacy and safety of LUMYKRAS have not been studied in patients with other oncogenic driver mutations (see "Warnings and precautions").

2.2.3 Requested Dosage

The recommended dosage of Lumykras is 960 mg (eight film-coated 120 mg tablets) orally once daily.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	22 April 2021
Formal control completed	22 April 2021
List of Questions (LoQ)	25 June 2021
Answers to LoQ	6 September 2021
Predecision	26 October 2021
Answers to Predecision	21 November 2021
Final Decision	16 December 2021
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

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3 Medical Context

NSCLC accounts for 80% of lung cancers, and adenocarcinoma is the most common histological subtype. The anticipated 5-year survival is approximately 26% for patients with clinical stage IIIB NSCLC and less than 5% for patients who present with clinical stage IV disease.

In NSCLC, KRAS is mutated in around one third of patients, much more frequently than other oncogenic drivers. KRAS p.G12C mutations predominate in NSCLC, accounting for 11%–16% of lung adenocarcinomas (45%–50% of mutant KRAS is p.G12C).
Based on the estimated incidence of the KRAS p.G12C mutation in NSCLC adenocarcinoma, the expected number of new cases diagnosed annually for KRAS p.G12C-mutated NSCLC is around 61,000 in Europe, and 300 in Switzerland.

Although the relevance of KRAS mutations in human cancers is known, KRAS p.G12C mutation inhibitors were difficult to develop. Despite enormous efforts to date, almost all identified compounds that could effectively and directly target mutant KRAS have failed.

Sotorasib appears to be a potent and selective KRASG12C inhibitor that covalently and irreversibly binds to the mutated cysteine of KRAS G12C.

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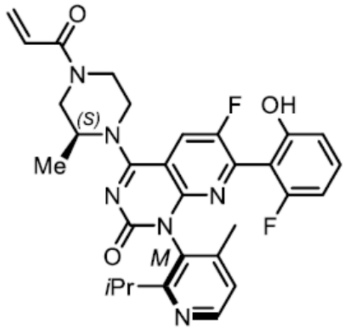
4 Quality Aspects

4.1 Drug Substance

INN: Sotorasib
Chemical name: 6-fluoro-7-(2-fluoro-6-hydroxyphenyl)-(1M)-1-[4-methyl-2-(propan-2-yl)pyridin-3-yl]-4-[(2S)-2-methyl-4-(prop-2-enoyl)piperazin-1-yl]pyrido[2,3-d]pyrimidin-2(1H)-one
Molecular formula: $C_{30}H_{30}F_2N_6O_3$
Molecular mass: 560.6 g/mol
Molecular structure:



Sotorasib is a white to off-white to yellow powder. It is practically insoluble in water.
It contains one asymmetric centre and one chiral axis and is manufactured as the (S,M)-enantiomer.
The drug substance is manufactured by a multi-step chemical synthesis with final isolation by crystallisation and a subsequent milling operation.
The drug substance specification includes relevant tests for proper quality control, encompassing e.g. tests relating to identification, assay, and impurities.
Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug Product

LUMYKRAS is an immediate-release, oral, solid dosage form at a strength of 120 mg. It is presented as a yellow, oblong (7 mm x 16 mm), film-coated tablet debossed with “AMG” on one side and “120” on the other.
The composition of the product is adequately described, qualitatively and quantitatively. LUMYKRAS contains lactose monohydrate.
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process.
The standard manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data, and including batch manufacturing formula and in-process controls.
The process validation of the commercial manufacturing process was successfully completed.
The drug product specification covers relevant physicochemical characteristics, as well as identification, assay and purity tests. They allow for proper control of the drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the finished product.
The finished product is packaged into blisters consisting of clear PVC/PE/PVDC-aluminium.
Appropriate stability data have been generated for the drug product in the packaging material intended for marketing and following the relevant international guidelines. The data show good stability of the finished drug product and allow for a distinct assignment of the shelf life.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Pharmacology

The binding of sotorasib to $KRAS^{G12C}$ was structurally characterised using X-ray crystallography. This structure confirmed the predicted binding to the P2 pocket of the inactive form of KRASG12C (KRASG12C-GDP) and the covalent bond formed between the acrylamide of sotorasib and the thiol of the substituted cysteine.
Sotorasib inhibited the association of the RAS-binding domain (RBD) with G12C-mutant KRAS (IC_{50} 0.09 µM), but did not inhibit RBD-binding to wild-type KRAS (IC_{50} > 250 µM). M18, which is the only metabolite retaining the covalent warhead of sotorasib, was less potent (IC_{50} 0.31 µM). Metabolites M24 and M10, which lack the warhead, showed minimal inhibition in the exchange assay (IC_{50} 123 µM and 78 µM).
Sotorasib was evaluated for its ability to inhibit the growth of KRAS p.G12C (NCI-H358 NSCLC and MIA PaCa-2 T2 pancreatic carcinoma) and KRAS p.G12V (SW480-1AC colorectal carcinoma) human tumour xenografts in athymic nude mice at doses from 0.3 to 200 mg/kg. Dose-related tumour growth inhibition and tumour regression occurred in the two KRAS G12C tumour xenograft models, but no effects on tumour growth were observed in xenografts with other KRAS mutants.
No relevant activity was observed *in vitro* on secondary targets including receptors, enzymes, ion channels, and transporters at concentrations up to 10 µM, which corresponds to 142-fold the unbound human C_{max}. The cysteine-proteome profiling in NCI-H358 cells showed that sotorasib engaged only the cysteine at amino acid position 12 (Cys12) in a peptide from $KRAS^{G12C}$.
The applicant conducted safety pharmacology studies to investigate potential effects on the cardiovascular system. The IC_{50} value for inhibition of the hERG channel was 54.8 µM. Considering the levels of unbound drug at the clinical dose (1.15 µM), it is unlikely that sotorasib affects heart repolarisation.
In conscious telemetered male dogs administered sotorasib at single oral doses up to 300 mg/kg, no effects were observed on electrocardiogram, heart rate, arterial pressures, left ventricular end diastolic pressure, or body temperature. However, the exposure at this dose was below the human exposure. No cardiovascular effects were observed in humans.
Specific studies on respiratory and central nervous system (CNS) function were not conducted, which is in line with ICH S9, and as no specific risks have been identified.

Pharmacokinetics

The pharmacokinetics of sotorasib was investigated after single intravenous and oral administration, as well as after repeated oral administration in mice, rabbits, rats, and dogs.
Sotorasib was rapidly absorbed in all species, with t_{max} ranging from 0.25 to 1.2 hours, similar to that in humans (1 hour).
The oral bioavailability was similar in rats and dogs (32% and 34%), 22% in normal mice, 46% in nude mice, and very low in monkeys (3.3%). Volume of distribution was moderate and varied from 0.6 to 2.3 L/kg (3.5 L/kg in humans), which suggests drug distribution into tissues. Sotorasib showed clearance varying from 1.43 to 5.24 L/h/kg across the species (0.44L/h/kg in humans). The terminal half-life in the test species ranged from 0.34 to 0.71 hours and was shorter than the $t_{1/2}$ in humans (5 hours).
In repeat-dose studies in rats and dogs, exposure to sotorasib increased in a generally proportional manner. There was no accumulation in rats, whereas some accumulation was observed dogs. There were no consistent sex-related differences in exposure of sotorasib in rats or dogs.
In a tissue distribution study with oral administration of 60 mg/kg ^{14}C-sotorasib to pigmented and albino rats, extensive distribution of drug-derived radioactivity was observed. Tissues with the highest radioactivity exposures in both rat strains were liver, kidney, thyroid, pancreas, exorbital lacrimal gland, and the intra-orbital lacrimal gland. Concentrations of radioactivity in the uveal tract and both pigmented and non-pigmented skin were low, and radioactivity was not quantifiable 48 hours post dose, indicating no affinity for melanin. Sotorasib showed limited distribution to the CNS.
Sotorasib plasma protein binding varied between species, with values of 29%, 46%, 79%, and 89%, respectively, in mice, rats, dogs, and humans.

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The blood-to-plasma partition ratios indicate that the majority of sotorasib is constrained to plasma in mice, rats, dogs, and humans.
The metabolism of sotorasib was examined *in vitro* in mouse, rat, dog, and human liver microsomes and hepatocytes. The metabolites M10 (cysteine conjugate derived from M12, glutathione conjugate), M18 (oxidation), and M24 (reduction and dealkylation) were the predominant metabolites formed using human hepatocytes. No unique human metabolites were observed.
In vitro studies using recombinant CYP enzymes demonstrated that CYP3A4 (primarily), CYP3A5, and CYP2C8 catalyse the metabolism of sotorasib.
The *in vivo* metabolism and excretion of sotorasib were investigated in rats and dogs after oral administration. [^{14}C]-sotorasib was administered as a single oral dose of 60 mg/kg in non-cannulated rats or in bile duct-cannulated rats. Sotorasib biotransformation was mediated primarily by non-enzymatic glutathione conjugation, oxidation and, to a lesser extent, reduction and dealkylation. Secondary metabolism was substantive and included amide hydrolysis, cleavage to yield cysteine conjugate, N-acetylation, methylation, glucuronidation, and sulfonation.
In rats, sotorasib was mainly excreted in faeces. Biliary excretion accounted for 66.3% of the administered dose. Metabolites in excreta were substantive and accounted for approximately 2% of dose in urine and approximately 60% of dose in faeces.
In dogs, sotorasib was the most abundant radioactive component in faeces for both sexes and accounted for almost 100% of the dose. This is comparable to the excretion of sotorasib in humans.
The passage into milk was not investigated. The recommendation for breastfeeding in the information for healthcare professionals is adequate.

Toxicology

The applicant conducted the toxicological evaluation of sotorasib in rats, rabbits, and dogs.
The oral route of administration as well as the duration of the studies in rodents and non-rodents support the clinical use.
Sotorasib was evaluated in toxicity studies with daily dosing for up to 3 months in rats (60, 180, or 750 mg/kg/day with a recovery period of 2 months) and dogs (100 or 500 mg/kg twice daily in order to achieve a higher systemic exposure).
The main target organs for toxicity were the haematopoietic system, kidney, liver, pituitary gland and thyroid. No NOAEL could be established in rats and dog studies. In rats, the severely toxic dose in 10% of the animals (STD 10) was established as 180 mg/kg, corresponding to an exposure 1.7-fold the clinical exposure. In dogs, the highest non-severely toxic dose was considered to be 1000 mg/kg/day, corresponding to an exposure below the clinical exposure.
Effects on the haematopoietic system included minimal to mild decreases in red blood cells in both species. The changes were reversible or showed partial recovery in rats.
Effects on kidney were observed in rats at the highest dose of 750 mg/kg/day. The findings included changes in urinalysis, clinical chemistry, and increases in urinary biomarkers of tubular injury. The effects on kidney are considered to be species-specific and related to metabolites, as disproportionally increased mercapturate pathway metabolites (M10 and M20) were detected in the renal tissue in rats at the nephrotoxic dose of 750 mg/kg/day compared to lower doses. Renal toxicity was not observed in clinical studies.
In dogs, effects were observed in the liver, pituitary gland, and thyroid gland at ≥ 200 mg/kg. Minimal to mild hypertrophy of centrilobular hepatocytes, correlating with increased liver weights and total bilirubin, and minimal to mild hypertrophy of pituitary basophils in the *pars distalis,* correlating with increased pituitary weight, were observed. Mild to moderate follicular cell hypertrophy and moderate to marked colloid depletion in the thyroid, correlating with decreased thyroid weight, were observed. Sotorasib induced increased mRNA expression of UGTs (UGT1A6 and UGT2B31), as well as CYP1A1 and CYP3A12 in dog hepatocytes. Therefore, liver, pituitary, and thyroid changes were considered adaptive or secondary responses to hepatocellular enzyme induction and secondary hypothyroidism, which can be accepted. Thyroid function was assessed clinically without adverse effects.

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The lack of safety margins can be accepted considering the proposed indication. The effects observed in rats and dogs are not considered of significant human risk based on the nature of findings and/or the lack of a signal in clinical trials. In addition, renal, liver, and thyroid effects can be monitored.
Fertility and early embryonic development studies were not conducted in accordance with ICH S9.
In the repeated dose toxicity studies in sexually mature animals, there were no adverse findings on female or male reproductive organs.
In embryo-fetal development studies, sotorasib did not cause adverse developmental effects in rats. In rabbits, once daily oral administration of sotorasib during the period of organogenesis resulted in lower maternal and fetal body weights, and a reduction in the number of ossified metacarpals was observed in fetuses at 100 mg/kg/day. At the NOAEL of 30 mg/kg/day, the exposure was below the clinical exposure. The recommendation in the “Pregnancy” section of the information for healthcare professionals is adequate.
Sotorasib was not genotoxic in a bacterial reverse mutation assay at concentrations up to 5000 µg/plate. In a combined *in vivo* mammalian erythrocyte micronucleus test and a comet assay conducted in rats, no effects were observed after oral doses of up to 2000 mg/kg for 4 days at exposures 10.9-fold the human clinical exposure.
Carcinogenicity studies were not conducted in accordance with ICH S9.
Sotorasib was not phototoxic *in vitro* in the 3T3 neutral red assay.
There are no concerns with regard to impurities or excipients.
Based on the ERA, sotorasib does not represent a risk for the environment at the prescribed dose.

Nonclinical conclusions

In conclusion, the pharmaco-toxicological profile of sotorasib is considered to be sufficiently well characterised. The submitted nonclinical data support the approval of Lumykras in the proposed indication. The relevant information has been included in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

ADME

Absorption
Following oral administration of sotorasib (AMG510) at doses of 180 - 960 mg, maximum sotorasib concentrations were reached after median times of 1-2 h, both, after single and multiple dose administration.
The absolute bioavailability has not been determined but is expected to be low (based on the results of a mass balance study) and dose-dependent (see dose linearity below).

Following administration of multiple once daily doses, sotorasib did not accumulate. In fact, the exposure after repeated administration was lower than after the first dose, with mean accumulation ratios ($AUC_{0\text{-}24h}$ ratio) ranging from 0.532 to 0.726. This time-dependent PK is consistent with autoinduction of sotorasib`s CYP3A4/5-dependent metabolism.

Bioequivalence was demonstrated between the administration of a single dose of 960 mg sotorasib as intact film-coated tablets (8 x 120-mg tablets) or as dispersed tablets in water.

Food effect
The effect of a high-fat meal on the bioavailability of sotorasib was assessed with the commercial formulation at a dose of 360 mg: Concomitant administration with food caused a delay in the median sotorasib t_{max} by 1.25 h (from 0.5 to 1.75 h). C_{max} values were unchanged, while mean $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ were increased to 1.4-fold in the fed state. As this food effect was only mild, sotorasib can be administered irrespective of meals.

Dose linearity
Sotorasib exhibits a pronounced less than dose-proportional PK. Based on comparisons across studies, no increase in exposure was observed, following administration of a single dose of 960 mg compared to a single dose of 360 mg in healthy subjects.
A similar effect was observed in patients across a dose range of 180 – 960 mg:
Following a single dose, sotorasib C_{max} and $AUC_{0\text{-}24h}$ increased 1.4- and 1.9-fold, respectively, across the dose range of 180 to 960 mg (5.3-fold increase in dose).
Similarly, following repeated administration for 8 days, sotorasib C_{max} and $AUC_{0\text{-}24h}$ increased only 1.0- and 1.3-fold, respectively, across the same dose range.
The limited, pH-dependent solubility of sotorasib likely contributed to the less than dose proportional PK. The contribution of additional factors, such as dose-dependent autoinduction, remained unclear.

This pronounced non-linearity in exposure raises concerns regarding the proposed dose of 960 mg. Furthermore, there is a risk of overdosing in cases where the factors responsible for the less than dose proportional increase in exposure change.

Distribution
Sotorasib and its metabolites do not distribute into blood cells, and in vitro plasma protein binding was 89%.
Based on in vitro data, sotorasib has a high membrane permeability. Transporters are therefore not expected to be relevant for the absorption or distribution of sotorasib.

Metabolism
Based on in vitro data, sotorasib is metabolised by CYP2C8 and CYP3A4/5 to the metabolites M24 (bond cleavage at the piperazine acrylamide moiety) and M18 (aromatic hydroxylation).

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In addition, M12, a glutathione conjugate formed primarily by non-enzymatic conjugation, M10, a cysteine adduct and downstream metabolite of glutathione conjugation, and other minor metabolites were found.

In a mass-balance study, following a single oral dose of 720 mg [^{14}C]-sotorasib, sotorasib and the metabolites M10, M18, M24 were identified as radioactive components in plasma. However, due to methodological issues, quantitative results varied between different analytical approaches.

Excretion
In the mass balance study, 74.4% of the radioactive dose was recovered in faeces, mostly in the form of unchanged sotorasib (52.97 % of the administered dose). Three metabolites in faeces each accounted for <5% of the radioactive dose. Only 5.81% of the administered dose was recovered in urine. Sotorasib had a mean terminal half-life of 6.8 h.

Special Populations / Intrinsic Factors
Potential effects of renal or hepatic impairment on the PK of sotorasib were not assessed in dedicated studies, but as part of the PopPK analysis.

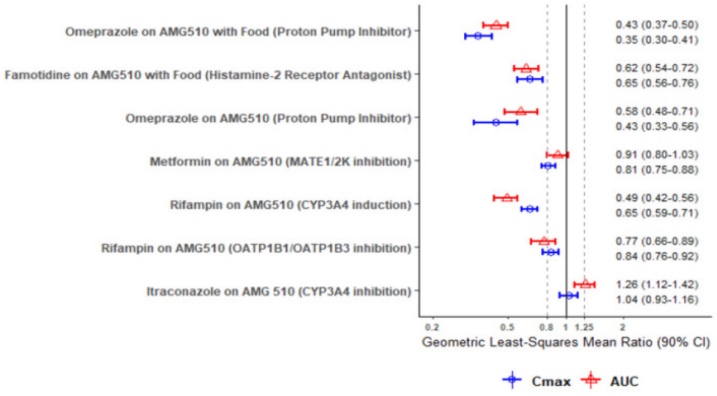
Renal impairment
The PopPK analyses indicated no significant effect of mild or moderate renal impairment on the PK of sotorasib. Considering the limited renal elimination of sotorasib, this result is in accordance with theoretical expectations. No dose adjustments are required in patients with mild or moderate renal impairment. No data from subjects/patients with GFR < 30 ml/min were available.

Hepatic impairment
The PopPK analyses indicated no significant effect of mild hepatic impairment on the PK of sotorasib. No data from subjects/patients with moderate or severe hepatic impairment were available. In light of the hepatic toxicity, the use of sotorasib is currently not recommended in these patient subgroups, and additional assessment of the PK and safety is required in order to establish an appropriate dose in these patients.

Based on the PopPK analysis, no dose adjustments were required based on age, gender or ethnicity.

Interactions
Effects of other drugs on sotorasib
The following graph summarizes the results of drug-drug interaction studies conducted with sotorasib as a victim.

Forest Plot of Sotorasib Drug-drug Interaction Studies with Sotorasib as a Victim



X-axis is represented on a $\log_2$ scale.

Source: applicant`s submitted documentation

CYP3A inducers and inhibitors
Sotorasib is primarily metabolised by CYP3A4 and CYP3A5, and the CYP3A inducer rifampicin reduced the exposure of sotorasib. In consequence, concomitant administration with CYP3A4 inducers is not recommended.

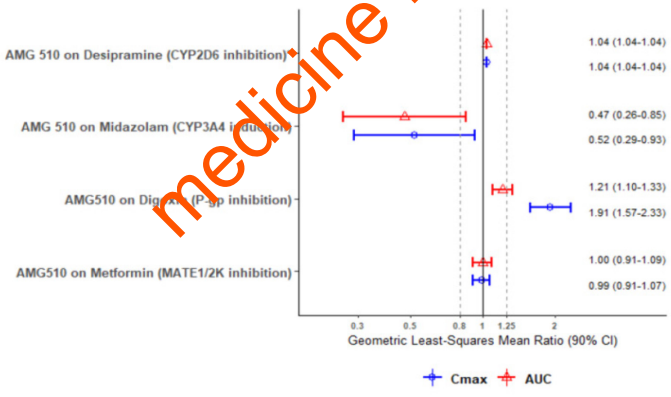
Concomitant administration of a single dose of 360 mg sotorasib with the CYP3A4/5 inhibitor itraconazole caused an increase in sotorasib AUC_{last} up to 1.35-fold and in AUC_{inf} up to 1.26-fold, while C_{max} was unaffected (1.040-fold) compared to administration of sotorasib alone. In principle, the study results are in agreement with theoretical expectations. However, since sotorasib has a dose- and time-dependent PK, a single dose interaction study is not adequate to fully assess the strength of the interaction under steady-state conditions.

Gastric pH modifying drugs
Sotorasib has a pH-dependent solubility, with moderate solubility under acidic conditions, but solubility decreases with increasing pH. Consequently, concomitant intake with drugs that elevate the gastric pH decreased the bioavailability of sotorasib (independently of concomitant intake with food).
Concomitant use with proton pump inhibitors or H2-receptor antagonists is not recommended. If treatment with a gastric pH modifying drug is required, intake of sotorasib 4 h before or 10 h after a local antacid is recommended.

Effects of sotorasib on other drugs

The following graph summarises the results of drug-drug interaction studies conducted with sotorasib as a perpetrator.

Forest Plot of Sotorasib Drug-drug Interaction Studies with Sotorasib as a Perpetrator



* PBPK model-predicted geometric mean ratios of Cmax and AUC for subjects with rapid extensive metabolizing CYP2D6 phenotype
X-axis is represented on a $\log_2$ scale.

Source: applicant`s submitted documentation

CYP3A substrates
Sotorasib is a moderate inducer of CYP3A4, causing decreased exposure of CYP3A4 substrates (e.g. midazolam). In consequence, concomitant use with CYP3A4 substrates with a narrow therapeutic window should be avoided. If concomitant use cannot be avoided, the dose of the CYP3A4 substrate should be adjusted.

P-gp substrates

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Sotorasib is a moderate inhibitor of P-gp, causing elevated exposure of P-gp substrate (e.g. digoxin). Concomitant use with narrow therapeutic index substrates should be avoided. If concomitant use cannot be avoided, the dose of the P-gp substrate should be reduced.

MATE1/2K substrates
In vitro data indicated that sotorasib has a potential to inhibit MATE1/2K. However, in an in vivo drug-drug interaction study with metformin, no relevant effect on the exposure of metformin was observed.

BCRP substrates
Based on in vitro data, sotorasib might cause a clinically relevant inhibition of BCRP. Assessment of this potential interaction in a clinical interaction study is required, and a respective study will be conducted by the applicant as a post-marketing commitment.

Other CYP enzymes
In vitro data indicate that sotorasib induces CYP2C8, CYP2C9 and CYP2B6. These interactions have not been assessed in clinical studies, and uncertainty remains about the clinical relevance.

Glutathione conjugation
Besides enzymatic elimination, sotorasib is also eliminated by non-enzymatic glutathione conjugation. Based on theoretical considerations, the risk of glutathione depletion due to normal doses of sotorasib alone is considered to be low. However, glutathione availability might become critical in special situations where the glutathione pool is already limited (e.g. administration of high doses of paracetamol). Therefore, cautious concomitant use is recommended for drugs whose elimination critically depends on glutathione.

Pharmacodynamics

Mechanism of Action and primary Pharmacology
Sotorasib is a first-in-class, irreversible inhibitor of the $KRAS^{G12C}$ mutant protein. The covalent, irreversible binding and inhibition of $KRAS^{G12C}$ by sotorasib requires a reactive thiol group adjacent to the sotorasib binding pocket. This thiol is provided by the cysteine at KRAS position 12 of the G12C mutant. Sotorasib contains a thiol reactive portion that covalently modifies the cysteine residue and locks $KRAS^{G12C}$ in an inactive guanosine diphosphate-bound conformation. This blocks the interaction of KRAS with its downstream signalling effectors.

Secondary Pharmacology (Safety)
An analysis of the relationship between sotorasib plasma concentration and change in QTcF from baseline, following administration of 960 mg sotorasib once daily, indicated that sotorasib did not cause a prolongation of the QT interval greater than the threshold of regulatory concern (20 msec). Potential effects at supratherapeutic exposures have not been investigated.

6.2 Dose Finding and Dose Recommendation

The requested dose of 960 mg once daily (QD) was evaluated in phase 1 of study 20170543 (CodeBreaK100). Phase 1 was divided into a dose exploration Part 1 and a dose expansion Part 2. The monotherapy safety analysis set for this phase-1 interim analysis included all subjects who received ≥ 1 dose of sotorasib and consisted of 124 subjects with $KRAS^{G12C}$-mutated NSCLC. Taking into account the limited number of patients treated with doses < 960 mg (ranging from 180 QD to 960 mg QD), no clear benefit compared to lower doses was shown for the recommended Phase 2 dose of 960 mg QD. Furthermore, sotorasib exhibited a pronounced, less than dose-proportional PK, resulting in almost comparable steady-state exposures across the dose range of 180-960 mg.

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The applicant adds a dose comparison part (Part B) to the phase-2 portion of the study CodeBreaK100 in order to determine the optimal dose in subjects with previously treated locally advanced and unresectable or metastatic $KRAS^{G12C}$ mutant advanced NSCLC. This substudy was initiated as a post approval requirement by the FDA. The FDA Multidisciplinary Review explains the rationale, providing five reasons for its conclusion that 960 mg is not considered to be the optimal dose: (1) There was no relationship between administered dose (across the entire 180-960 mg dose range) and drug exposure at steady state, (2) there was no evidence of a relationship between dose and response rate, (3) gastrointestinal toxicities may be reduced at a lower dose, (4) preclinical data suggest that the minimal effective dose is 30-240 mg daily, and (5) the labelled dose requires patients to take eight tablets at a time, which is a burden on patients.

The applicant confirmed submission of the results of this substudy as a condition for the temporary authorisation (post-marketing commitment Study 20170543 Phase 2 Part B).

6.3 Efficacy

For evaluation of efficacy and safety, the applicant submitted results of study 20170543 (CodeBreaK 100, Phase 2).

Overall, 126 adult patients (≥ 18 years) with previously treated $KRAS^{G12C}$-mutated locally advanced or metastatic NSCLC were included in study CodeBreaK 100 phase 2. Patients with NSCLC must have progressed after receiving anti-PD1 or anti-PD-L1 immunotherapy (unless contraindicated) AND/OR platinum-based combination chemotherapy AND targeted therapy if actionable oncogenic driver mutations were identified (i.e., EGFR, ALK, and ROS1). Subjects must have received no more than three prior lines of therapy. Patients with untreated active brain metastases were excluded.
The number of patients is limited for a valid evaluation of efficacy and safety, in particular taking into account the fact that KRAS mutations represent one of the most common oncogenic driver mutations in lung cancer. However, despite enormous efforts to date, almost all identified compounds that could effectively and directly target mutant KRAS have failed. Because of the medical need for targeted therapies for this mutation, the number of included patients is acceptable for a temporary authorisation.

Primary endpoint was Objective Response Rate (ORR) measured by computed tomography (CT) or magnetic resonance imaging (MRI) and assessed per response evaluation criteria in solid tumours (RECIST 1.1). Response was assessed by blinded independent central review, and complete response (CR) and partial response (PR) required confirmatory CT or MRI repeat assessment at least 4 weeks after the first detection of response. Relevant secondary endpoints were duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

A total of 224 subjects were enrolled in phase 2, of whom 126 subjects had NSCLC. Included patients with NSCLC had a median age of 63.5 years (range 37-80), 50% were male, 81.7% were White and 69.8% had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 (30.2% had ECOG 0). At screening 96% had stage IV disease and only four patients had disease stage III. Of these four subjects with stage III NSCLC at study entry, two (50%) achieved a partial response with sotorasib treatment, a third subject achieved a tumour reduction of 28%. All four subjects had prior therapies that included chemo-radiation, platinum-doublet chemotherapy, and/or immunotherapy. Taken into account the fact that these patients had unresectable NSCLC and had already received systemic anticancer therapy, treatment options are limited. Therefore, it can be accepted that the indication will not be restricted to patients with metastatic disease.

In addition, 99% had a non-squamous histology - a total of five subjects with squamous cell histology were enrolled in study CodeBreaK 100 (four subjects in the phase 1 portion and one in phase 2). This is in line with a recent analysis using up-to-date differential diagnostic criteria suggesting that KRAS

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mutations do not occur in pure pulmonary squamous cell lung carcinomas, and in detected cases, were confined to lung adenocarcinoma components in squamous cancer (Ghimessy et al. Cancer Metastasis Rev. 2020). Of the five subjects with squamous cell histology, four patients received prior anticancer therapy for metastatic disease. None of these four subjects achieved a response; two subjects had a best response of stable disease and one had progressive disease. Therefore, the indication is restricted to non-squamous metastatic NSCLC.

According to the inclusion criteria, 100% had a $KRAS^{G12C}$ mutation (99.2% centrally confirmed). By central testing no other actionable alterations were identified in the study.
At baseline, 26.2% had PD-L1 expression < 1%, 19% ≥1% - < 50% and 27.8% ≥ 50%, for an additional 27% the PD-L1 status was unknown.

The median number of prior lines was two, 42.9% had one prior line, 34.9% had two prior lines and 22.2% three prior lines of therapy (maximum three prior lines). Overall, 91.3% had prior chemotherapy (89.7% platinum-based chemotherapy), 92.1% prior therapy with an immune checkpoint inhibitor (91.3% PD-1/PD-L1) and 81% had both platinum-based chemotherapy and PD-1/PD-L1 (not specified if combined or across different lines). In addition, 23.8% had targeted therapies, 19.8% anti-VEGF (vascular epithelial growth factor) therapy. According to the inclusion criteria, all patients had to have progressive disease after IO and/or platinum chemotherapy and target therapy.

Results for NSCLC (cut-off 1st December 2020):
Of a total of 126 subjects with NSCLC, 123 subjects were included in the full analysis set, and three subjects were excluded as they did not have ≥ 1 measurable lesion according to a blinded independent central review (BICR).

The **ORR** in patients with NSCLC was 37.1%, 4% had a CR and 34.7% a PR. Among the 46 objective responders who had NSCLC, the Kaplan-Meier estimate of median DOR was 10 months (95% CI 1.2, 11.1). ORR results are supported by the phase 1 results. The outcome in patients with advanced NSCLC on second- or third-line therapies is poor, with response rates of <20%. Therefore, the results of CodeBreaK100 are clinically promising. However, confirmatory data of an adequately designed controlled study are needed, particularly taking into account the anticipated resistance to KRAS inhibitors. Currently, a randomised, open label, active-controlled phase III trial is ongoing to evaluate AMG 510 (sotorasib) versus docetaxel for the treatment of previously treated locally advanced and unresectable or metastatic NSCLC with mutated $KRAS^{G12C}$ (post-marketing commitment study 20190009, CodeBreak 200, NCT04303780).
ORR in subjects receiving both platinum-based chemotherapy AND anti-PD1/anti-PD-L1 was 32%. The ORR was 28% if platinum-based chemotherapy AND anti-PD1/anti-PD-L1 were combined and 36% if platinum-based chemotherapy AND anti-PD1/anti-PD-L1 were administered in different lines of therapy.

The median (range) follow-up time for PFS was 11.0 (0.3, 12.6) months. As of the data cut-off date, the percentages of subjects in the full analysis set of the phase 2 NSCLC group with an event of disease progression or death were 56.5% and 10.5%, respectively. The median PFS was 6.8 months. The median (range) follow-up time for OS was 12.2 (1.1, 15.6) months. As of the data cut-off date, of the 126 subjects in the phase 2 NSCLC safety analysis set, 59 subjects (46.8%) died and 67 subjects (53.2%) were censored. The median OS was 12.5 months.

Results for PFS and OS in a single arm study should be interpreted with caution. However, median PFS of 6.8 months and median OS of 12.5 months are clinically promising in comparison to historical results. However, further results from a confirmatory trial are necessary.

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6.4 Safety

Overall, 427 patients were included in the monotherapy safety analysis set. Of these, 383 patients (89.7%) took 960 mg sotorasib, including 339 patients with sotorasib 960 mg once daily in the fasted state, 18 patients took sotorasib 960 mg once daily in the fed state and 26 patients sotorasib 480 mg twice a day in the fed state.
Analyses of monotherapy safety did not demonstrate a dose-dependent increase in adverse events. However, since the results in patients with doses < 960 mg are limited, no valid conclusion is possible.

Overall, a total of 224 subjects received ≥ 1 dose of sotorasib and were included in the phase 2 safety analysis set of study CodeBreaK 100, Phase 2.

All adverse events summarised in the text are treatment-emergent, defined as occurring after the first dose of sotorasib through 30 days after the last dose of sotorasib.

In total, 99.2% of the patients had a treatment emergent adverse event (TEAE). Most common TEAEs (≥10%) were diarrhoea, nausea, fatigue, aspartate aminotransferase (ASAT) increased, alanine aminotransferase (ALT) increased, dyspnoea, vomiting, constipation, back pain, blood alkaline phosphatase increased, peripheral oedema, cough, decreased appetite, pleural effusion.

Overall, 56.3% had TEAEs ≥ grade 3. Most common (≥5%) ≥ grade 3 TEAEs were ASAT increased, ALAT increased, pleural effusion, pneumonia, diarrhoea and dyspnoea.

In total, 50% of the patients had serious adverse events (SAEs). Most common (≥5%) SAEs were observed in the system organ classes (SOCs) gastrointestinal disorders, infections and infestations (pneumonia 7.1%), musculoskeletal and connective tissue disorders (back pain 3.2%), neoplasms benign, malignant and unspecified (NSCLC 6.3%), respiratory, thoracic and mediastinal disorders (pleural effusion 4.8%)

Overall, 31 grade 5 events (13.2%) were observed. No subject had a fatal adverse event that was considered to be related to the investigational product by the investigator. Of these, 20 events occurred in the NSCLC patient group, including two cardiac disorders (one cardiac arrest, one cardiac failure), one gastric ulcer, one systemic inflammatory response syndrome, 12 neoplasms (nine NSCLC, two malignant lung neoplasms, one adenocarcinoma, one bronchial carcinoma), two cases of respiratory failure and one of hypovolaemic shock. Grade 5 events that occurred in patients with other tumour entities included one small intestinal obstruction, one cholangitis and nine neoplasms (one colon cancer, one cholangiocarcinoma, one endometrial adenocarcinoma, one large cell lung cancer, one malignant neoplasm of unknown primary site, four pancreatic carcinomas).

Female patients with NSCLC treated with sotorasib 960 mg once daily in the fasted state (n=102) had a higher rate of grade 3-4 events, SAEs and grade 5 events (19.6% vs.12.5%) compared to male patients (n=88). This aspect is described in the information for healthcare professionals, “Undesirable effects” section.

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6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Clinical Pharmacology
Sotorasib has the potential for clinically relevant interactions, which limits its concomitant use with inducers of CYP3A, gastric pH modifying drugs and with sensitive substrates of CYP3A and P-gp. Based on in vitro data, there is also a risk of a clinically relevant inhibition of BCRP. Additional assessment of the clinical relevance of this interaction is required (post-marketing commitment).

Sotorasib has not been investigated in patients with severe renal impairment. However, due to the limited renal elimination of sotorasib, cautious use in these patients is acceptable.

Sotorasib has not been investigated in patients with moderate or severe hepatic impairment. In light of the hepatic toxicity, sotorasib is currently not recommended in these patients. Additional assessment of the PK and safety in order to establish an appropriate dose in these patients is required (post-marketing commitment).

Clinical
There are no approved therapies in Switzerland specifically for patients with NSCLC and $KRAS^{G12C}$ mutation. Patients with $KRAS^{G12C}$ NSCLC are currently treated with combined chemo-immunotherapy (IO) and, if IO is contraindicated, platinum-based chemotherapy.

The efficacy provided with this submission demonstrated compelling ORR. However, results for efficacy and safety are limited due to low numbers and the absence of a comparator arm and further data are necessary. In addition, the dose of sotorasib 960 mg once daily has not been adequately studied compared to lower doses and needs to be explored in the dose comparison part of study CodeBreaK100.

Given the unmet medical need in patients with advanced NSCLC with $KRAS^{G12C}$ mutation, a temporary authorisation can be granted.

Relevant safety risks are interstitial lung disease (ILD)/pneumonitis and hepatotoxicity (including drug-induced liver injury and hepatitis). These risks are adequately described in the information for healthcare professionals. However, further long-term safety data are needed.

In the context of the temporary authorisation in accordance with Art. 9a TPA, conditions to be fulfilled for an ordinary authorisation were defined. Taking into account the concerns regarding dose and the limited efficacy and safety data, the applicant has to submit the following clinical data as a condition. The temporary authorisation is subject to the timely submission of the results of the 20170543 Phase 2 Part B study (dose comparison part) and the results of the ongoing Phase III study 20190009 (CodeBreaK200). In addition, the final results of study CodebreaK100 have to be submitted.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Lumykras was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions. LUMYKRAS is temporarily authorised – see "Properties/Effects" section.

LUMYKRAS®

Composition

Active substances

Sotorasib.

Excipients

Tablet core: Microcrystalline cellulose, lactose monohydrate (114 mg per tablet), croscarmellose sodium (corresponds to max. 1.6 mg sodium per tablet), magnesium stearate.

Film-coating: Polyvinyl alcohol, titanium dioxide, macrogol 4000, talc, iron oxide yellow.

Pharmaceutical form and active substance quantity per unit

Film-coated tablet with 120 mg sotorasib per film-coated tablet.

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

Indications/Uses

LUMYKRAS is indicated as monotherapy for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic non-squamous non-small cell lung cancer (NSCLC) who have experienced progression after prior treatment with platinum-based chemotherapy and/or anti-PD-1/PD-L1 immunotherapy (see “Clinical efficacy”).

The efficacy and safety of LUMYKRAS has not been studied in patients with other oncogenic driver mutations (see "Warnings and precautions").

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Dosage/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.

Usual dosage

The recommended dose of LUMYKRAS is 960 mg (eight 120 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.

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 (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

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Table 2. Recommended dose modifications for sotorasib

Adverse reaction	Severity[a]	Dose modification
Elevated liver enzymes	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 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

Co-administration of LUMYKRAS with other agents

There are restrictions and special dosing instructions for the concomitant use of LUMYKRAS with other medicines which are described in section “Interactions”.

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Special dosage instructions

Patients with hepatic disorders

No dose adjustment is recommended for patients with mild hepatic impairment (AST or ALT < 2.5 × ULN or total bilirubin < 1.5 × ULN). LUMYKRAS has not been studied in patients with moderate or severe hepatic impairment (see “Pharmacokinetics”) and should not be used in these patients.

Patients with renal disorders

No dose adjustment is recommended for patients with mild and moderate renal impairment (creatine clearance (CrCL) ≥ 30 mL/min). However, since data are limited in patients with moderate renal impairment, caution should be exercised when treating these patients (see “Pharmacokinetics”).

LUMYKRAS has not been studied in patients with severe renal impairment (CrCL < 30 mL/min). Therefore, caution should be exercised when treating patients with severe or end stage renal impairment (see “Pharmacokinetics”).

Elderly patients

Of the 359 patients in clinical studies who received the recommended dose of LUMYKRAS of 960 mg once daily, 40% were ≥ 65 years of age and 8% were ≥ 75 years of age. No overall differences in safety or efficacy were observed in comparison with younger patients. No dose adjustment is required based on age (see “Pharmacokinetics”).

Children and adolescents

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

Mode of administration

LUMYKRAS is for oral use. The tablets must be swallowed whole and should not be chewed, crushed, or split.

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 tablets are dispersed into small

pieces (the tablet will not completely dissolve) and drink 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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section “Composition”.

Warnings and precautions

Hepatotoxicity

LUMYKRAS can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis. In clinical studies, elevations of ALT and AST occurred (see “Undesirable effects”). 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. Monitor liver function tests (ALT, AST, 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 who develop transaminase and/or bilirubin elevations. Withhold, dose reduce or permanently discontinue LUMYKRAS based on severity of adverse reaction (see “Dosage/Administration”, table 2).

Interstitial Lung Disease (ILD)/pneumonitis

ILD/pneumonitis occurred in patients treated with LUMYKRAS with prior exposure to immunotherapy or radiotherapy (see “Undesirable Effects”). 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 “Dosage/Administration”).

Concomitant oncogenic driver mutations

The efficacy and safety of LUMYKRAS has not been studied in patients with other oncogenic driver mutations.

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'.

Interactions

Effect of other medicinal products on sotorasib

Concomitant use is not recommended

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% (Geometric Mean Ratio (GMR): 0.35 [90% CI: 0.30, 0.41]) and AUC by 57% (GMR: 0.43 [90% CI: 0.37, 0.50]). 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% (GMR: 0.65 [90% CI: 0.56, 0.76]) and AUC by 38% (GMR: 0.62 [90% CI: 0.54, 0.72]).

Under fasted conditions, co-administration of multiple doses of omeprazole with a single dose of 960 mg sotorasib decreased sotorasib C_{max} by 57% (GMR: 0.43 [90% CI: 0.33, 0.56]) and AUC by 42% (GMR: 0.58 [90% CI: 0.48, 0.71]).

Co-administration of PPIs and H_2 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 "Dosage/Administration").

Strong CYP3A4 inducers

Co-administration of sotorasib with multiple doses of a strong CYP3A4 inducer (rifampicin) decreased sotorasib C_{max} by 35% (GMR: 0.65 [90% CI: 0.59, 0.71]) and AUC by 51% (GMR: 0.49 [90% CI: 0.42,

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0.56]). Co-administration of strong CYP3A4 inducers with LUMYKRAS is not recommended because the impact on sotorasib efficacy is unknown.

Other interactions

CYP3A4 inhibitors

No clinically relevant effect on sotorasib exposure was observed following the concomitant use of a single dose of LUMYKRAS with itraconazole (a combined strong CYP3A4 inhibitor and P-gp inhibitor). The influence of strong CYP3A4 inhibition in steady-state on sotorasib has not been investigated. Due to the time-dependent kinetics of sotorasib, an interaction cannot be excluded.

Transporter systems

No clinically meaningful effect on the exposure of sotorasib was observed following co-administration of LUMYKRAS with a single dose of rifampicin (an OATP1B1/1B3 inhibitor), or metformin (a MATE1/MATE2-K substrate).

Effect of sotorasib on other medicinal products

Concomitant use is not recommended

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% (GMR: 0.52 [90% CI: 0.29, 0.93]) and AUC by 53% (GMR: 0.47 [90% CI: 0.28, 0.79]).

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 medicinal product information.

P-glycoprotein (P-gp) Substrates

Co-administration of LUMYKRAS with a P-gp substrate (digoxin) increased digoxin plasma concentrations by 91% for C_{max} (GMR: 1.91 [90% CI: 1.57, 2.33]) and 21% for AUC (GMR: 1.21 [90% CI: 1.11, 1.33]) which may increase the adverse reactions of digoxin. Co-administration of LUMYKRAS with P-gp substrates for which minimal concentration changes may lead to serious

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toxicities is not recommended. If co-administration cannot be avoided, decrease the P-gp substrate dosage in accordance with its medicinal product information.

Glutathione-dependent elimination

Sotorasib is eliminated by non-enzymatic conjugation with glutathione, among other routes. Interactions with the elimination of other medicinal products degraded by this route have not been studied. Caution should be exercised when sotorasib is co-administered with medicinal products whose elimination critically depend on the available amount of glutathione (e.g. paracetamol).

Other interactions

Transporter systems

In vitro data indicated that sotorasib may have the potential to inhibit Breast Cancer Resistance Protein (BCRP); the clinical relevance of these findings is unknown. When LUMYKRAS is co-administered with BCRP substrates (e.g., methotrexate, mitoxantrone, topotecan and lapatinib), appropriate monitoring is recommended.

Co-administration of sotorasib with metformin (a sensitive MATE1/2K substrate) did not decrease metformin exposures (GMR for C_{max}: 1.00 [90% CI: 0.91, 1.09]; GMR for AUC: 0.99 [90% CI: 0.91, 1.07]). Co-administration of LUMYKRAS with MATE1/2K substrates is not anticipated to impact the PK of MATE1/2K substrates.

In vitro studies indicate that sotorasib is an inhibitor of human organic anion transporter (OAT)3 and OATP1B1. The clinical relevance of these findings is unknown.

Substrates of PXR regulated enzymes

In vitro studies indicate that sotorasib may induce pregnane X receptor (PXR) regulated enzymes (e.g. CYP2C family and UGT). Co-administration of sotorasib with CYP2C8, CYP2C9 or CYP2C19 substrates may decrease their exposure.

CYP enzymes

In vitro studies showed that sotorasib can induce CYP2B6. Sotorasib had no inhibitory effect on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 *in vitro*.

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Pregnancy, lactation

Pregnancy

There are no data from the use of sotorasib in pregnant women. Studies in animals have shown reproductive toxicity (see “Preclinical data”). LUMYKRAS should not be used during pregnancy unless the women’s clinical condition requires treatment with sotorasib. 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.

Lactation

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

It is not known whether sotorasib affects the ability of humans to reproduce.

Effects on ability to drive and use machines

No corresponding studies have been performed. Fatigue and nausea may occur during treatment with LUMYKRAS. The patient must be informed accordingly and advised not to drive in these cases.

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 undesirable effects were diarrhoea (34%), musculoskeletal pain (28%), nausea (25%), and fatigue (21%). The most common severe (grade ≥ 3) undesirable effects were increased ALT (5%), increased AST (4%), and diarrhoea (4%). The most common undesirable effects leading to permanent discontinuation of treatment were increased ALT (1%) and increased AST (1%). The most common undesirable effects leading to dose modification were increased ALT (6%), increased AST (6%), and diarrhoea (6%).

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List of undesirable effects

Undesirable effects 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 (≥ 1/1000 to < 1/100), rare (≥ 1/10'000 to < 1/1000), very rare (< 1/10'000). Within each system organ class, undesirable effects are presented in order of decreasing frequency.

Table 3. Undesirable effects

MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)
Infections and infestations		Pneumonia	
Blood and lymphatic system disorders	Anaemia (13%)	Lymphocytes decreased	Increased activated partial thromboplastin time
Metabolism and nutrition disorders		Decreased appetite	
Nervous system disorders	Headache (10%)		
Respiratory, thoracic and mediastinal disorders	Cough (11%) Dyspnoea (11%)		ILD/pneumonitis
Gastrointestinal disorders	Diarrhoea (34%) Nausea (25%) Vomiting (18%) Constipation (13%) Abdominal pain (13%)[a]		

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MedDRA system organ class	Very common (≥ 1/10)	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1000 to < 1/100)
Hepatobiliary disorders	Aspartate aminotransferase increased (16%) Alanine aminotransferase increased (14%)	Drug-induced liver injury Blood alkaline phosphatase increased Blood bilirubin increased Gamma-glutamyltransferase increased	
Skin and subcutaneous tissue disorders		Rash	
Musculoskeletal and connective tissue disorders	Arthralgia (14%) Musculoskeletal pain (28%)[b]		
General disorders and administration site conditions	Fatigue (24%) Edema (12%)[c] Pyrexia (10%)		

[a] Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower
[b] Musculoskeletal pain includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, and pain in extremity
[c] Edema includes generalized edema, localized edema, edema, edema peripheral, periorbital edema, and testicular edema

Description of specific undesirable effects and additional information

Elevated Liver Enzymes

In clinical studies, transient elevations of serum transaminases were observed (see “Warnings and precautions”). Elevations of ALT occurred in 14% of subjects and elevations of AST in 16% of subjects, with a median time to onset of 8 weeks (range: 1 to 42) and 8 weeks (range: 0 to 42), respectively. No cases of liver failure or fatal cases were observed in clinical studies.

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ILD/pneumonitis

In clinical studies, among 359 patients who received LUMYKRAS, 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 (see “Dosage/Administration” and “Warnings and precautions”).

Safety depending on gender

Female patients with NSCLC treated with LUMYKRAS 960 mg QD fasted (n = 108) had a higher rate of grade 3-4 undesirable effects (59.3% vs. 54.3%), serious undesirable effects (57.4% vs. 46.7%), grade 5 undesirable effects (20.4% vs.14.1%) compared to male patients (n = 92).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

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.

Pharmacodynamics

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

LUMYKRAS for the treatment of previously treated KRAS G12C-mutated NSCLC (CodeBreaK 100)

The efficacy of LUMYKRAS was evaluated in a single-arm, open-label, multicentre trial (CodeBreaK 100) that enrolled patients with locally advanced or metastatic *KRAS G12C*-mutated NSCLC and other solid tumours who had disease progression after receiving prior therapy. For patients with NSCLC, 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, not more than 3 prior lines of therapy, 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 with NSCLC 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) defined as the proportion of patients who achieved complete response (CR) or partial response (PR) as evaluated by a BICR according to RECIST v1.1. Additional efficacy outcome measures included duration of response (DOR), 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.

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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.

The ORR was 37.1% (95% CI: 28.6, 46.2), with 2.4% of patients achieving a CR and 34.7% a PR. The patients with objective responses had a median DOR of 10.0 months (range: 1.2 to 11.1 months). The ORR for patients with brain metastases was 15.4% (95% CI: 4.4, 34.9).

Median PFS was 6.8 months (95% CI: 5.1, 8.2). Disease progression or death occurred in 56.5% and 10.5% of patients, respectively. The median follow-up time for PFS was 11.0 months.

Median OS was 12.5 months (95% CI: 10, not estimable). 46.8% of the patients had died. The median follow-up time for OS was 12.2 months.

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 lead to a large mean increase in QTc interval (> 20 msec). Possible effects of supratherapeutic exposure have not been investigated.

Temporary authorisation

The medicinal product LUMYKRAS has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Pharmacokinetics

Absorption

Following an oral, single-dose administration, sotorasib was absorbed with median time to achieve peak concentration of 1 hour. The absolute bioavailability of sotorasib has not been determined. Sotorasib systemic exposure was comparable between film-coated tablets and film-coated tablets predispersed in water administered under fasted conditions.

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.

Distribution

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

Metabolism

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

In vitro data indicate that sotorasib is metabolised by CYP2C8, 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.

Elimination

At 960 mg once daily, the steady state apparent clearance is 26.2 L/hr. The mean half-life is 5 hours. Sotorasib is primarily eliminated in faeces with approximately 74% of the dose recovered in faeces (53% unchanged) and 6% (1% unchanged) recovered in urine.

Linearity / non-linearity

Sotorasib exhibited non-linear, time-dependent, pharmacokinetics over the dose range of 180 mg to 960 mg once daily with similar systemic exposure (i.e. $AUC_{0\text{-}24h}$ and C_{max}) across doses at steady state, likely due to low solubility. Steady state was reached within 22 days. No accumulation was observed after repeat sotorasib dosages with a mean accumulation ratio of 0.56 (coefficient of variation (CV): 59%).

Kinetics in specific patient groups

No clinically meaningful differences in the pharmacokinetics of sotorasib were observed based on age, sex, race or ethnicity, body weight, line of therapy, or ECOG PS.

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Hepatic impairment

Based on a population PK analysis (n = 413 with normal hepatic function; n = 83 with mild hepatic impairment), no clinically meaningful differences in the pharmacokinetics of sotorasib were observed in patients with mild hepatic impairment (AST or ALT < 2.5 × ULN or total bilirubin < 1.5 × ULN). The effect of moderate to severe hepatic impairment on sotorasib pharmacokinetics has not been studied.

Renal impairment

Based on a population PK analysis (n = 199 with normal renal function; n = 255 with mild renal impairment; n = 37 with moderate renal impairment), no clinically meaningful differences in the pharmacokinetics of sotorasib were observed in patients with mild and moderate renal impairment (CrCL: ≥ 30 mL/min). The effect of severe renal impairment on sotorasib pharmacokinetics has not been studied.

Preclinical data

Repeated dose toxicity

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 due to local formation of a putative sulfur-containing metabolite than humans.

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). Although thyroid levels were not measured in dogs, induction of uridine diphosphate glucuronosyltransferase known to be involved in thyroid hormone metabolism was confirmed in the *in vitro* dog hepatocyte assay.

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

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.

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 (at exposure 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.

Other information

Incompatibilities

None.

Shelf life

The medicinal product may only be used until the date marked "EXP" on the pack.

Special precautions for storage

Do not store above 30°C.

Special precautions for disposal

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

Authorisation number

67693 (Swissmedic)

Packs

Packs of 240 film-coated tablets. [A]

Marketing authorisation holder

Amgen Switzerland AG, Risch; Domicile: 6343 Rotkreuz

Date of revision of the text

December 2021

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