Prescription only

LUMAKRAS™ tablets 120mg

(sotorasib)

[COMPOSITION]

1 tablet (618.0 mg) contains

Active Ingredient: Sotorasib (in-house) 120.0 mg

Excipients: Microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, Magnesium stearate, Opadry II Yellow(85F120132)

[APPEARANCE]

Yellow, oblong, film-coated tablet

[INDICATION]

Treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), who have received at least one prior therapy.
The efficacy of THIS DRUG was based on overall response rate (ORR) and duration of response (DOR), and there are no data demonstrating overall survival (OS) in the confirmatory trial.

[DOSAGE AND ADMINISTRATION]

1 KRAS G12C test

If THIS DRUG is administered, the KRAS G12C mutation status should be evaluated prior to initiation of treatment using a sufficiently validated and reliable test method.

2 Recommended Dosage

THIS DRUG is administered as 960 mg (eight 120 mg tablets) orally once daily until disease progression or unacceptable toxicity.

Take THIS DRUG at the same time each day with or without food. Swallow tablets whole. Do not chew, crush or split tablets. If a dose of THIS DRUG is missed by more than 6 hours, take the next dose as prescribed the next day. Do not take 2 doses at the same time to make up for the missed dose.

If vomiting occurs after taking THIS DRUG, do not take an additional dose. Take the next dose as prescribed the next day.

3 Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablets in 120 mL of room-temperature water without crushing. No other liquids should be used. Stir until tablets are dispersed into small pieces (the tablets will not completely dissolve) and drink immediately or within 2 hours. The appearance of the mixture may range from pale yellow to bright yellow. Swallow the tablet dispersion. Do not chew pieces of the tablet in the dispersion. Rinse the container with an additional 120 mL of water and drink. If the mixture is not consumed immediately, stir the mixture again to ensure that tablets are dispersed.

4 Dosage Modifications for Adverse Reactions

THIS DRUG dose reduction levels are summarized in Table 1. Dosage modifications for adverse reactions are provided in Table 2.

If adverse reactions occur, a maximum of two dose reductions are permitted. Discontinue THIS DRUG if patients are unable to tolerate the minimum dose of 240 mg once daily.

Table 1. Recommended THIS DRUG Dose Reduction Levels for Adverse Reactions

Dose Reduction Level	Dose
First dose reduction	480 mg (4 tablets) once daily
Second dose reduction	240 mg (2 tablets) once daily

Table 2. Recommended THIS DRUG Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity[a]	Dosage Modification
Hepatotoxicity	Grade 2 AST or ALT with symptoms or Grade ≥ 3 AST or ALT	• Withhold THIS DRUG until recovery to ≤ Grade 1 or to baseline grade. • Resume THIS DRUG at the next lower dose level.
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	• Permanently discontinue THIS DRUG.

Adverse Reaction	Severity[a]	Dosage Modification
Interstitial Lung Disease (ILD)/pneumonitis	Any Grade	• Withhold THIS DRUG if ILD/pneumonitis is suspected. • Permanently discontinue THIS DRUG if ILD/pneumonitis is confirmed.
Nausea or vomiting despite appropriate supportive care (including anti-emetic therapy)	Grade 3 to 4	• Withhold THIS DRUG until recovery to ≤ Grade 1 or to baseline grade. • Resume THIS DRUG at the next lower dose level.
Diarrhea despite appropriate supportive care (including anti-diarrheal therapy)	Grade 3 to 4	• Withhold THIS DRUG until recovery to ≤ Grade 1 or to baseline grade. • Resume THIS DRUG at the next lower dose level.
Other adverse reactions	Grade 3 to 4	• Withhold THIS DRUG until recovery to ≤ Grade 1 or to baseline grade. • Resume THIS DRUG at the next lower dose level.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal

[a] Grading defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0

5 Coadministration of THIS DRUG with Acid-Reducing Agents

Avoid coadministration of proton pump inhibitors (PPIs) and H2 receptor antagonists with THIS DRUG. If treatment with an acid-reducing agent cannot be avoided, take THIS DRUG 4 hours before or 10 hours after administration of a local antacid

[PRECAUTIONS FOR USE]

1. Warning

Interstitial Lung Disease (ILD)/Pneumonitis

THIS DRUG can cause ILD/pneumonitis that can be fatal. Among 357 patients who received THIS DRUG in clinical trials (CodeBreaK 100). ILD/pneumonitis occurred in 0.8% of patients, all cases were Grade 3 or 4 at onset, and 1 case was fatal. The median time to first onset for ILD/pneumonitis was 2 weeks (range: 2 to 18 weeks). THIS DRUG was discontinued due to ILD/pneumonitis in 0.6% of patients. Monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold THIS DRUG in patients with suspected ILD/pneumonitis and permanently discontinue THIS DRUG if no other potential causes of ILD/pneumonitis are identified.

2. Contraindications to the following patients

Patients with known hypersensitivity to active ingredient of THIS DRUG or to any component of the product formulation.

B. Since this drug contains lactose, it should not be administered to patients with genetic problems such as galactose intolerance, Lap lactase deficiency, or glucose-galactose malabsorption.

3. Careful Administration

Hepatotoxicity

THIS DRUG can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis. Among 357 patients who received THIS DRUG in CodeBreaK 100, hepatotoxicity occurred in 1.7% (all grades) and 1.4% (Grade 3). A total of 18% of patients who received THIS DRUG had increased alanine aminotransferase (ALT)/increased aspartate aminotransferase (AST); 6% were Grade 3 and 0.6% were Grade 4. The median time to first onset of increased ALT/AST was 9 weeks (range: 0.3 to 42). Increased ALT/AST leading to dose interruption or reduction occurred in 7% of patients. THIS DRUG was discontinued due to increased ALT/AST in 2.0% of patients. In addition to dose interruption or reduction, 5% of patients received corticosteroids for the treatment of hepatotoxicity.

Monitor liver function tests (ALT, AST, and total bilirubin) prior to the start of THIS DRUG, 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 THIS DRUG based on severity of adverse reaction.

4. Adverse Reactions

The safety of THIS DRUG was evaluated in a subset of patients with KRAS G12C-mutated locally advanced or metastatic NSCLC in CodeBreaK 100. Patients received THIS DRUG 960 mg orally once daily until disease progression or unacceptable toxicity (n = 204). Among patients who received THIS DRUG, 39% were exposed for 6 months or longer and 3% were exposed for greater than one year.

The median age of patients who received THIS DRUG was 66 years (range: 37 to 86); 55% female; 80% White, 15% Asian, and 3% Black.

Serious adverse reactions occurred in 50% of patients treated with THIS DRUG. Serious adverse reactions in ≥ 2% of patients were pneumonia (8%), hepatotoxicity (3.4%), and diarrhea (2%). Fatal adverse reactions occurred in 3.4% of patients who received THIS DRUG due to respiratory failure (0.8%), pneumonitis (0.4%), cardiac arrest (0.4%), cardiac failure (0.4%), gastric ulcer (0.4%), and pneumonia (0.4%). .

Permanent discontinuation of THIS DRUG due to an adverse reaction occurred in 9% of patients. Adverse reactions resulting in permanent discontinuation of THIS DRUG in ≥ 2% of patients included hepatotoxicity (4.9%).

Dose interruptions of THIS DRUG due to an adverse reaction occurred in 34% of patients. Adverse reactions which required dosage interruption ≥ 2% were hepatotoxicity (11%), diarrhea (8%), musculoskeletal pain (3.9%), nausea (2.9%), and pneumonia (2.5%).

Dose reductions of THIS DRUG due to an adverse reaction occurred in 5% of patients. Adverse reactions which required dose reductions in > 2% of patients included increased ALT (2.9%) and increased AST (2.5%).

The most common adverse reactions ≥ 20% were diarrhea, musculoskeletal pain, nausea, fatigue, hepatotoxicity, and cough. The most common laboratory abnormalities ≥ 25% were decreased lymphocytes, decreased hemoglobin, increased aspartate aminotransferase, increased alanine aminotransferase, decreased calcium, increased alkaline phosphatase, increased urine protein, and decreased sodium.

Table 3 summarizes the common adverse reactions observed in CodeBreaK 100.

Table 3. Adverse Reactions (≥ 10%) %) of Patients With KRAS G12C Mutated NSCLC Who Received THIS DRUG in CodeBreaK 100[*]

Adverse Reaction	THIS DRUG N = 204	
	All Grades (%)	Grade 3 to 4 (%)
Gastrointestinal disorders		
Diarrhea	42	5
Nausea	26	1
Vomiting	17	1.5
Constipation	16	0.5
Abdominal pain[a]	15	1.0
Hepatobiliary disorders		
Hepatotoxicity[b]	25	12
Respiratory		
Cough[c]	20	1.5
Dyspnea[d]	16	2.9
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[e]	35	8
Arthralgia	12	1.0
General disorders and administration site conditions		
Fatigue[f]	26	2.0
Edema[g]	15	0
Metabolism and nutrition disorders		
Decreased appetite	13	1.0
Infections and infestations		
Pneumonia[h]	12	7
Skin and subcutaneous tissue disorders		
Rash[i]	12	0

[*] Grading defined by NCI CTCAE version 5.0

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

[b] Hepatotoxicity includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatitis, transaminases abnormal, transaminases increased

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

[d] Dyspnea includes dyspnea and dyspnea exertional

[e] 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

[f] Fatigue includes fatigue and asthenia

[g] Edema includes generalized edema, localized edema, edema, edema peripheral, periorbital edema, and testicular edema.

[h] Pneumonia includes pneumonia, pneumonia aspiration, pneumonia bacterial, and pneumonia staphylococcal

[i] Rash includes dermatitis, dermatitis acneiform, rash, rash-maculopapular, rash pustular

Table 4 summarizes the selected laboratory adverse reactions observed in CodeBreaK 100.

Table 4. Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With KRAS G12C-Mutated NSCLC Who Received THIS DRUG in CodeBreak 100

Laboratory Abnormalities	THIS DRUG N = 204*	
	Grades 1 to 4 (%)	Grades 3 to 4 (%)
Chemistry		
Increased aspartate aminotransferase	39	9
Increased alanine aminotransferase	38	11
Decreased calcium	35	0
Increased alkaline phosphatase	33	2.5
Increased urine protein	29	3.9
Decreased sodium	28	1.0
Decreased albumin	22	0.5
Hematology		
Decreased lymphocytes	48	2
Decreased hemoglobin	43	0.5
Increased activated partial thromboplastin time	23	1.5

* N = number of patients who had at least one on-study assessment for the parameter of interest.

5. General Cautions

Diagnosis of KRAS G12C mutated non-small cell lung cancer is needed to select patients to receive THIS DRUG. The evaluation of KRAS G12C mutated non-small cell lung cancer should be performed in laboratories that are proficient in the use of these technologies.
In clinical trials (CodeBreak 100), QIAGEN therascreen® KRAS RGQ PCR was used to diagnose KRAS G12C mutated non-small cell lung cancer.

6. Drug-Drug Interactions

A. Acid-Reducing Agents

Coadministration of THIS DRUG with gastric acid-reducing agents decreased sotorasib concentrations which may reduce the efficacy of sotorasib. Avoid coadministration of THIS DRUG with proton pump inhibitors (PPIs), H2 receptor antagonists, and locally acting antacids. If coadministration with an acid-reducing agent cannot be avoided, administer THIS DRUG 4 hours before or 10 hours after administration of a locally acting antacid.

B. Strong CYP3A4 Inducers

Coadministration of THIS DRUG with a strong CYP3A4 inducer decreased sotorasib concentrations, which may reduce the efficacy of sotorasib. Avoid coadministration of THIS DRUG with strong CYP3A4 inducers.

C. CYP3A4 Substrates

Coadministration of THIS DRUG with a CYP3A4 substrate decreased its plasma concentrations, which may reduce the efficacy of the substrate. Avoid coadministration of THIS DRUG with CYP3A4 sensitive substrates, for which minimal concentration changes may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, increase the sensitive CYP3A4 substrate dosage in accordance with its Prescribing Information.

D. P-glycoprotein (P-gp) Substrates

Coadministration of THIS DRUG with a P-gp substrate (digoxin) increased digoxin plasma concentrations, which may increase the adverse reactions of digoxin. Avoid coadministration of THIS DRUG with P-gp substrates for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the P-gp substrate dosage in accordance with its Prescribing Information.

7. Use in Pregnancy, Nursing Mothers, Pediatric Population, and Geriatric Population

A. Pregnancy

There are no available data on THIS DRUG use in pregnant women. In rat and rabbit embryo-fetal development studies, oral sotorasib did not cause adverse developmental effects or embryo-lethality at exposures up to 4.6 times the human exposure at the 960 mg clinical dose.

B. Lactation

There are no data on the presence of sotorasib or its metabolites in human milk, the effects on the breastfed child, or on milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with THIS DRUG and for 1 week after the final dose.

C. Pediatric Use

The safety and effectiveness of THIS DRUG have not been established in pediatric patients.

D. Geriatric Use

Of the 357 patients with any tumor type who received THIS DRUG 960 mg orally once daily in CodeBreaK 100, 46% were 65 and over, and 10% were 75 and over. No overall differences in safety or effectiveness were observed between older patients and younger patients.

8. Renal Impairment

No clinically meaningful differences in the pharmacokinetics in patients with mild and moderate renal impairment (estimated glomerular filtrate rate (eGFR): ≥ 30 mL/min/1.73 m^2). THIS DRUG has not been studied in patients with severe renal impairment (eGFR: < 30 mL/min/1.73 m^2).

9. Hepatic Impairment

No clinically meaningful differences in the pharmacokinetics in patients with mild hepatic impairment (AST or ALT <2.5 x ULN or total bilirubin < 1.5 x ULN). THIS DRUG has not been studied in patients with moderate or severe hepatic impairment.

10. Cautions for Storage and Handling

A. Keep it out of reach of children.
B. Be careful not to replace it in other containers because it is not desirable in terms of quality or cause of accident.

11. Information for Health Care Providers

1) Pharmacological Action

Mechanism of Action

Sotorasib is an inhibitor of KRAS G12C, a tumor-restricted, mutant-oncogenic form of the RAS GTPase, KRAS. Sotorasib forms an irreversible, covalent bond with the unique cysteine of KRAS G12C, locking the protein in an inactive state that prevents downstream signaling without affecting wild type KRAS. Sotorasib blocked KRAS signaling, inhibited cell growth,

promoted apoptosis only in KRAS G12C tumor cell lines. Sotorasib inhibited KRASG12C *in vitro* and *in vivo* with minimal detectable off-target activity. In mouse tumor xenograft models, sotorasib-treatment led to tumor regressions and prolonged survival, and was associated with anti-tumor immunity in KRAS G12C models.

Cardiac Electrophysiology

At the approved recommended dosage, THIS DRUG does not cause large mean increases in the QTc interval (>20 msec).

2) Pharmacokinetics Information

The pharmacokinetics of sotorasib have been characterized in healthy subjects and in patients with KRAS G12C mutated solid tumors, including NSCLC.. Sotorasib exhibited non-linear, time-dependent, pharmacokinetics over the dose range of 180 mg to 960 mg (0.19 to 1 time the approved recommended dosage) once daily with similar systemic exposure (i.e., $AUC_{0\text{-}24h}$ and C_{max}) across doses at steady-state. Sotorasib systemic exposure was comparable between film-coated tablets and film-coated tablets predispersed in water administered under fasted conditions. Sotorasib plasma concentrations reached steady state within 22 days. No accumulation was observed after repeat THIS DRUG dosages with a mean accumulation ratio of 0.56 (coefficient of variation (CV): 59%).

Absorption

The median time to sotorasib peak concentration is 1 hour.

Effect of Food

When 960 mg THIS DRUG was administered with a high-fat, high-calorie meal (containing approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate and fat, respectively) in patients, sotorasib $AUC_{0\text{-}24h}$ increased by 25% compared to administration under fasted conditions.

Distribution

The mean volume of distribution (Vd) at steady state of sotorasib is 211 L (CV: 135%). In vitro, plasma protein binding of sotorasib is 89%.

Elimination

The sotorasib mean terminal elimination half-life is 5 hours (standard deviation (SD): 2). At 960 mg THIS DRUG once daily, the sotorasib steady state apparent clearance is 26.2 L/hr (CV: 76%).

Metabolism
The main metabolic pathways of sotorasib are non-enzymatic conjugation and oxidative metabolism with CYP3As.

Excretion
After a single dose of radiolabeled sotorasib, 74% of the dose was recovered in feces (53% unchanged) and 6% (1% unchanged) in urine.

Specific Populations
No clinically meaningful differences in the pharmacokinetics of sotorasib were observed based on age (28 to 86 years), sex, race (White, Black and Asian), body weight (36.8 to 157.9 kg), line of therapy, ECOG PS (0, 1).

Drug Interaction Studies

Clinical Studies
Acid Reducing Agents: Coadministration of repeat doses of omeprazole (PPI) with a single dose of THIS DRUG decreased sotorasib C_{max} by 65% and AUC by 57% under fed conditions, and decreased sotorasib C_{max} by 57% and AUC by 42% under fasted conditions. Coadministration of a single dose of famotidine (H2 receptor antagonist) given 10 hours prior to and 2 hours after a single dose of THIS DRUG under fed conditions decreased sotorasib C_{max} by 35% and AUC by 38%.

Strong CYP3A4 Inducers: Coadministration of repeat doses of rifampin (a strong CYP3A4 inducer) with a single dose of THIS DRUG decreased sotorasib C_{max} by 35% and AUC by 51%.

Other Drugs: No clinically meaningful effect on the exposure of sotorasib was observed following coadministration of THIS DRUG with itraconazole (a combined strong CYP3A4 and P gp inhibitor) and a single dose of rifampin (an OATP1B1/1B3 inhibitor), or metformin (a MATE1/MATE2 K substrate).

CYP3A4 substrates: Coadministration of THIS DRUG with midazolam (a sensitive CYP3A4 substrate) decreased midazolam C_{max} by 48% and AUC by 53%.

P gp substrates: Coadministration of THIS DRUG with digoxin (a P gp substrate) increased digoxin C_{max} by 91% and AUC by 21%.

MATE1/MATE2 K substrates: No clinically meaningful effect on the exposure of metformin (a MATE1/MATE2 K substrate) was observed following coadministration of THIS DRUG.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Sotorasib may induce CYP2C8, CYP2C9 and CYP2B6. Sotorasib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6.
Transporter Systems: Sotorasib may inhibit BCRP.

3) CLINICAL STUDIES

The efficacy of THIS DRUG was demonstrated in a subset of patients enrolled in a single arm, open-label, multicenter trial (CodeBreaK 100 [NCT03600883]). Eligible patients were required to have locally advanced or metastatic KRAS G12C-mutated NSCLC with disease progression after receiving an immune checkpoint inhibitor and/or platinum based chemotherapy, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, and at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

All patients were required to have prospectively identified KRAS G12C-mutated NSCLC in tumor tissue samples by using the QIAGEN therascreen® KRAS RGQ PCR Kit performed in a central laboratory. Of 126 total enrolled subjects, 2 (2%) were unevaluable for efficacy analysis due to the absence of radiographically measurable lesions at baseline. Of the 124 patients with KRAS G12C mutations confirmed in tumor tissue, plasma samples from 112 patients were tested retrospectively using the Guardant360® CDx. 78/112 patients (70%) had KRAS G12C mutation identified in plasma specimen, 31/112 patients (28%) did not have KRAS G12C mutation identified in plasma specimen and 3/112 (2%) were unevaluable due to Guardant360® CDx test failure.

A total of 124 patients had at least one measurable lesion at baseline assessed by Blinded Independent Central Review (BICR) according to RECIST v1.1 and were treated with THIS DRUG 960 mg once daily until disease progression or unacceptable toxicity. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) as evaluated by BICR according to RECIST v1.1.

The baseline demographic and disease characteristics of the study population were: median age 64 years (range: 37 to 80) with 48% ≥ 65 years and 8% ≥ 75 years; 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, 23% 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 5.

Table 5. Efficacy Results for Patients with KRAS G12C mutated NSCLC Who Received THIS DRUG in CodeBreak 100

Efficacy Parameter	THIS DRUG N=124
Objective Response Rate (95% CI)[a]	36 (28, 45)
Complete response rate, %	2
Partial response rate, %	35
Duration of Response[a]	
Median[b], months (range)	10.0 (1.3+, 11.1)
Patients with duration ≥ 6 months[c], %	58%

CI = confidence interval

[a] Assessed by Blinded Independent Central Review (BICR)

[b] Estimate using Kaplan-Meier method

[c] Observed proportion of patients with duration of response beyond landmark time

4) TOXICOLOGY

a) Carcinogenesis and Mutagenesis

Carcinogenicity studies have not been performed with sotorasib.

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

b) Impairment of Fertility

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

In a rat embryo-fetal development study, once daily oral administration of sotorasib to pregnant rats during the period of organogenesis resulted in maternal toxicity at the 540 mg/kg dose level [approximately 4.6 times the human exposure based on area under the curve (AUC) at the clinical dose of 960 mg]. Sotorasib did not cause adverse developmental effects and did not affect embryo-fetal survival at doses up to 540 mg/kg.

In a rabbit embryo-fetal development study, once daily oral administration of sotorasib during the period of organogenesis resulted in lower fetal body weights, and a reduction in the number of ossified metacarpals, in fetuses at the 100 mg/kg dose level (approximately 2.6 times the human exposure based on AUC at the clinical dose of 960 mg), which was associated with maternal toxicity including decreased body weight gain and food consumption during the dosing phase. Sotorasib did not cause adverse developmental effects and did not affect embryo-fetal survival at doses up to 100 mg/kg.

c) Toxicology

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

[STORAGE CONDITION]

Tight container, Stored at room temperature (1~30°C)

[PACKAGING UNIT]

240 tablets/carton (8 tablets/PTP x 30)

[EXPIRY DATE]

Refer to the outer package (Year/Month/Date)

[MARKETING APPLICATION HOLDER]

Amgen Inc. One Amgen Center Drive, Thousand Oaks, CA 91320, USA

[MANUFACTURER]

Patheon Inc. 2100 Syntex Court, Mississauga, Ontario L5N 7K9, Canada

[IMPORTER]

Amgen Korea Limited 20th floor, Eulji-ro 5-gil 19, Jung-gu, Seoul, Korea

- If products are decomposed, deteriorated, damaged, contaminated or expired, they can be exchanged at the pharmacy, clinic, hospital, or wholesaler where purchased. Please contact the facility where you bought the product for return or exchange.
- You will be compensated for consumers' damages as per the Consumer Injury Compensation Rule
- Application for Remedy for Side Effects of Drugs: The Korea Institute of Drug Safety and Risk Management (Tel: 1644-6223, www.drugsafe.or.kr)
- You can find the latest product information after the following revision date on the MFDS on-line library website (http://nedrug.mfds.go.kr) or the importer website (www.amgen.co.kr)
- Importer contact phone: 00798 611 3554 (toll free) / 02-3434-4899 / Medinfo.JAPAC@amgen.com

Revision date: 2022.02.14

Version No.: KRLUMPI01