HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LUMAKRAS safely and effectively. See full prescribing information for LUMAKRAS.

LUMAKRAS® (sotorasib) tablets, for oral use
Initial U.S. Approval: 2021

----------RECENT MAJOR CHANGES----------
Dosage and Administration (2.2, 2.3) 01/2023

----------INDICATIONS AND USAGE----------
LUMAKRAS is an inhibitor of the RAS GTPase family indicated for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy. (1)

This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1)

----------DOSAGE AND ADMINISTRATION----------
- Recommended dosage: 960 mg orally once daily. (2.2)
- Swallow tablets whole with or without food. (2.2)

----------DOSAGE FORMS AND STRENGTHS ----------
Tablets: 320 mg, 120 mg (3)

----------CONTRAINDICATIONS ----------
None. (4)

----------WARNINGS AND PRECAUTIONS ----------
- Hepatotoxicity: Monitor liver function tests every 3 weeks for the first 3 months of treatment then once monthly as clinically indicated. Withhold, reduce dose, or permanently discontinue LUMAKRAS based on the severity. (2.3, 5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Monitor for new or worsening pulmonary symptoms. Immediately withhold LUMAKRAS for suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified. (2.3, 5.2)

----------ADVERSE REACTIONS ----------
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. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Inc. at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS ----------
- Acid-Reducing Agents: Avoid coadministration with proton pump inhibitors (PPIs) and H_2 receptor antagonists. If an acid-reducing agent cannot be avoided, administer LUMAKRAS 4 hours before or 10 hours after a local antacid. (2.4, 7.1)
- Strong CYP3A4 Inducers: Avoid coadministration with strong CYP3A4 inducers. (7.1)
- CYP3A4 Substrates: Avoid coadministration with CYP3A4 substrates for which minimal concentration changes may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, adjust the substrate dosage in accordance to its Prescribing Information. (7.2)
- P-gp substrates: Avoid coadministration with P-gp substrates for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the substrate dosage in accordance to its Prescribing Information. (7.2)

----------USE IN SPECIFIC POPULATIONS ----------
Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LUMAKRAS is indicated for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test *[see Dosage and Administration (2.1)],* who have received at least one prior systemic therapy.

This indication is approved under accelerated approval based on overall response rate (ORR) and duration of response (DOR) *[see Clinical Studies (14)].* Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for treatment of locally advanced or metastatic NSCLC with LUMAKRAS based on the presence of *KRAS G12C* mutation in tumor or plasma specimens *[see Clinical Studies (14)].* If no mutation is detected in a plasma specimen, test tumor tissue.

Information on FDA-approved tests for the detection of *KRAS G12C* mutations is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage and Administration

The recommended dosage of LUMAKRAS is 960 mg (three 320 mg tablets or eight 120 mg tablets) orally once daily until disease progression or unacceptable toxicity.

Take the daily dose of LUMAKRAS at the same time each day with or without food *[see Clinical Pharmacology (12.3)]*. Swallow tablets whole. Do not chew, crush or split tablets. If a dose of LUMAKRAS 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 LUMAKRAS, do not take an additional dose. Take the next dose as prescribed the next day.

Administration to Patients Who Have Difficulty Swallowing Solids

Disperse tablets in 120 mL (4 ounces) of non-carbonated, room-temperature water without crushing. No other liquids should be used. Stir or swirl the cup for approximately 3 minutes 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. Rinse the container with an additional 120 mL (4 ounces) of water and drink. If the mixture is not consumed immediately, stir the mixture again to ensure that tablets are dispersed.

2.3 Dosage Modifications for Adverse Reactions

LUMAKRAS 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 LUMAKRAS if patients are unable to tolerate the minimum dose of 240 mg once daily.

Table 1. Recommended LUMAKRAS Dose Reduction Levels for Adverse Reactions

Dose Reduction Level	Dose
First dose reduction	480 mg (four 120 mg tablets) once daily
Second dose reduction	240 mg (two 120 mg tablets) once daily

Table 2. Recommended LUMAKRAS Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity[a]	Dosage Modification
Hepatotoxicity *[see Warnings and Precautions (5.1)]*	Grade 2 AST or ALT with symptoms or Grade 3 to 4 AST or ALT	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline. • Resume LUMAKRAS at the next lower dose level.
	AST or ALT > 3 × ULN with total bilirubin > 2 × ULN in the absence of alternative causes	• Permanently discontinue LUMAKRAS.
Interstitial Lung Disease (ILD)/ pneumonitis *[see Warnings and Precautions (5.2)]*	Any Grade	• Withhold LUMAKRAS if ILD/pneumonitis is suspected. • Permanently discontinue LUMAKRAS if ILD/pneumonitis is confirmed.
Nausea or vomiting despite appropriate supportive care (including anti-emetic therapy) *[see Adverse Reactions (6.1)]*	Grade 3 to 4	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline. • Resume LUMAKRAS at the next lower dose level.
Diarrhea despite appropriate supportive care (including anti-diarrheal therapy) *[see Adverse Reactions (6.1)]*	Grade 3 to 4	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline. • Resume LUMAKRAS at the next lower dose level.
Other adverse reactions *[see Adverse Reactions (6.1)]*	Grade 3 to 4	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline. • Resume LUMAKRAS 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

2.4 Coadministration of LUMAKRAS with Acid-Reducing Agents

Avoid coadministration of proton pump inhibitors (PPIs) and H_2 receptor antagonists with LUMAKRAS. If treatment with an acid-reducing agent cannot be avoided, take LUMAKRAS 4 hours before or 10 hours after administration of a local antacid *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 320 mg, beige, oval shaped, immediate release, film coated, debossed with “AMG” on one side and “320” on the opposite side.

Tablets: 120 mg, yellow, oblong-shaped, immediate release, film-coated, debossed with “AMG” on one side and “120” on the opposite side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatotoxicity

LUMAKRAS can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis. Among 357 patients who received LUMAKRAS in CodeBreaK 100 *[see Adverse Reactions (6.1)]*, hepatotoxicity occurred in 1.7% (all grades) and 1.4% (Grade 3). A total of 18% of patients who received LUMAKRAS 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. LUMAKRAS 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 LUMAKRAS, 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 LUMAKRAS based on severity of adverse reaction *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

5.2 Interstitial Lung Disease (ILD)/Pneumonitis

LUMAKRAS can cause ILD/pneumonitis that can be fatal. Among 357 patients who received LUMAKRAS in CodeBreaK 100 *[see Adverse Reactions (6.1)],* 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). LUMAKRAS 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 LUMAKRAS in patients with suspected ILD/pneumonitis and permanently discontinue LUMAKRAS if no other potential causes of ILD/pneumonitis are identified *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Hepatotoxicity *[see Warnings and Precautions (5.1)]*
- Interstitial Lung Disease (ILD)/Pneumonitis *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to LUMAKRAS as a single agent at 960 mg orally once daily in 357 patients with NSCLC and other solid tumors with *KRAS G12C* mutation enrolled in CodeBreaK 100, 28% were exposed for 6 months or longer and 3% were exposed for greater than one year.

Non-Small Cell Lung Cancer

The safety of LUMAKRAS was evaluated in a subset of patients with *KRAS G12C*-mutated locally advanced or metastatic NSCLC in CodeBreaK 100 *[see Clinical Studies (14)]*. Patients received LUMAKRAS 960 mg orally once daily until disease progression or unacceptable toxicity (n = 204). Among patients who received LUMAKRAS, 39% were exposed for 6 months or longer and 3% were exposed for greater than one year.

The median age of patients who received LUMAKRAS 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 LUMAKRAS. 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 LUMAKRAS 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 LUMAKRAS due to an adverse reaction occurred in 9% of patients. Adverse reactions resulting in permanent discontinuation of LUMAKRAS in ≥ 2% of patients included hepatotoxicity (4.9%).

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

Dose reductions of LUMAKRAS 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 LUMAKRAS in CodeBreaK 100*

Adverse Reaction	LUMAKRAS N = 204	
	All Grades (%)	Grades 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, thoracic, and mediastinal disorders		
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, and abdominal pain lower.
[b] Hepatotoxicity includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatitis, hepatotoxicity, liver function test increased, and 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, and 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 LUMAKRAS in CodeBreaK 100

Laboratory Abnormalities	**LUMAKRAS 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.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on LUMAKRAS

Acid-Reducing Agents

The solubility of sotorasib is pH-dependent. Coadministration of LUMAKRAS with gastric acid-reducing agents decreased sotorasib concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of sotorasib. Avoid coadministration of LUMAKRAS with proton pump inhibitors (PPIs), H_2 receptor antagonists, and locally acting antacids. If coadministration with an acid-reducing agent cannot be avoided, administer LUMAKRAS 4 hours before or 10 hours after administration of a locally acting antacid *[see Dosage and Administration (2.4)]*.

Strong CYP3A4 Inducers

Sotorasib is a CYP3A4 substrate. Coadministration of LUMAKRAS with a strong CYP3A4 inducer decreased sotorasib concentrations *[see Clinical Pharmacology (12.3)],* which may reduce the efficacy of sotorasib. Avoid coadministration of LUMAKRAS with strong CYP3A4 inducers.

7.2 Effects of LUMAKRAS on Other Drugs

CYP3A4 Substrates

Sotorasib is a CYP3A4 inducer. Coadministration of LUMAKRAS with a CYP3A4 substrate decreased its plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of the substrate. Avoid coadministration of LUMAKRAS 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.

P-glycoprotein (P-gp) Substrates

Sotorasib is a P-gp inhibitor. Coadministration of LUMAKRAS with a P-gp substrate increased its plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the adverse reactions of the substrate. Avoid coadministration of LUMAKRAS with P-gp substrates, for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the P-gp substrate dosage in accordance with its Prescribing Information.

Breast Cancer Resistance Protein (BCRP) Substrates

Sotorasib is a BCRP-inhibitor. Coadministration of LUMAKRAS with a BCRP substrate increased its plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions of the substrate. When coadministered with LUMAKRAS, monitor for adverse reactions of the BCRP substrate and decrease the BCRP substrate dosage in accordance with its Prescribing Information.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on LUMAKRAS 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 *(see Data)*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

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.

8.2 Lactation

Risk Summary

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 LUMAKRAS and for 1 week after the final dose.

8.4 Pediatric Use

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

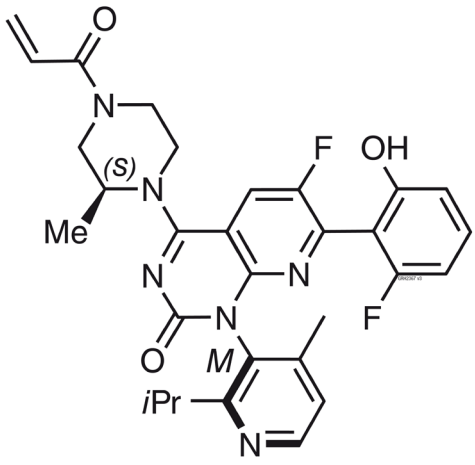
8.5 Geriatric Use

Of the 357 patients with any tumor type who received LUMAKRAS 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.

11 DESCRIPTION

Sotorasib is an inhibitor of the RAS GTPase family. The molecular formula is $C_{30}H_{30}F_2N_6O_3$, and the molecular weight is 560.6 g/mol. The chemical name of sotorasib is 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.

The chemical structure of sotorasib is shown below:



Sotorasib has pKa values of 8.06 and 4.56. The solubility of sotorasib in the aqueous media decreases over the range pH 1.2 to 6.8 from 1.3 mg/mL to 0.03 mg/mL.

LUMAKRAS is supplied as film-coated tablets for oral use containing 320 mg or 120 mg of sotorasib. Inactive ingredients in the tablet core are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The film coating material consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow and iron oxide red (320 mg tablet only).

12 CLINICAL PHARMACOLOGY

12.1 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, and promoted apoptosis only in *KRAS G12C* tumor cell lines. Sotorasib inhibited $KRAS^{G12C}$ *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.

12.2 Pharmacodynamics

Sotorasib exposure-response relationships and the time course of the pharmacodynamic response are unknown.

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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 LUMAKRAS dosages with a mean accumulation ratio of 0.56 (coefficient of variation (CV): 59%).

Absorption

The median time to sotorasib peak plasma concentration is 1 hour.

Effect of Food

When 960 mg LUMAKRAS 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 sotorasib mean volume of distribution (V_d) at steady state is 211 L (CV: 135%). *In vitro*, sotorasib plasma protein binding is 89%.

Elimination

The sotorasib mean terminal elimination half-life is 5 hours (standard deviation (SD): 2). At 960 mg LUMAKRAS 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), mild and moderate renal impairment (eGFR: ≥ 30 mL/min/1.73 m^2), or mild hepatic impairment (AST or ALT < 2.5 × ULN or total bilirubin < 1.5 × ULN). The effect of severe renal impairment or moderate to severe hepatic impairment on sotorasib pharmacokinetics has not been studied.

Drug Interaction Studies

Clinical Studies

Acid-Reducing Agents: Coadministration of repeat doses of omeprazole (PPI) with a single dose of LUMAKRAS 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 (H_2 receptor antagonist) given 10 hours prior to and 2 hours after a single dose of LUMAKRAS 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 LUMAKRAS 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 LUMAKRAS 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 LUMAKRAS with midazolam (a sensitive CYP3A4 substrate) decreased midazolam C_{max} by 48% and AUC by 53%.

P-gp substrates: Coadministration of LUMAKRAS 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 LUMAKRAS.

BCRP substrates: Coadministration of LUMAKRAS with rosuvastatin (a BCRP substrate) increased rosuvastatin C_{max} by 70% and AUC by 34%.

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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with sotorasib.

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

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.

13.2 Animal Toxicology and/or Pharmacology

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.

14 CLINICAL STUDIES

The efficacy of LUMAKRAS 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 LUMAKRAS 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 LUMAKRAS in CodeBreaK 100

Efficacy Parameter	LUMAKRAS 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

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

LUMAKRAS (sotorasib) 320 mg tablets are beige, oval shaped, film coated, debossed with "AMG" on one side and "320" on the opposite side are supplied as follows:

- Carton containing one bottle of 90 tablets with child-resistant closure, NDC 55513-504-50

LUMAKRAS (sotorasib) 120 mg tablets are yellow, oblong-shaped, film-coated, debossed with "AMG" on one side and "120" on the opposite side are supplied as follows:

- Carton containing two bottles of 120 tablets with child-resistant closure, NDC 55513-488-02
- Carton containing one bottle of 240 tablets with child-resistant closure, NDC 55513-488-24

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F). Excursions permitted from 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hepatotoxicity

Advise patients to immediately contact their healthcare provider for signs and symptoms of liver dysfunction *[see Warnings and Precautions (5.1)]*.

Interstitial Lung Disease (ILD)/Pneumonitis

Advise patients to contact their healthcare provider immediately to report new or worsening respiratory symptoms *[see Warnings and Precautions (5.2)]*.

Lactation

Advise women not to breastfeed during treatment with LUMAKRAS and for 1 week after the final dose *[see Use in Specific Populations (8.2)]*.

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, dietary and herbal products. Inform patients to avoid proton pump inhibitors, and H_2 receptor antagonists while taking LUMAKRAS *[see Drug Interactions (7.1) and (7.2)]*.

If coadministration with an acid-reducing agent cannot be avoided, inform patients to take LUMAKRAS 4 hours before or 10 hours after a locally acting antacid *[see Dosage and Administration (2.4)]*.

Missed Dose

If a dose of LUMAKRAS is missed by greater than 6 hours, resume treatment as prescribed the next day *[see Dosage and Administration (2.2)]*.

AMGEN®

LUMAKRAS® (sotorasib)
Manufactured by:
Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799 U.S.A.
Patent: http://pat.amgen.com/lumakras/

1XXXXXX – V3

PATIENT INFORMATION
LUMAKRAS® (loo-ma-krass)
(sotorasib) tablets

What is LUMAKRAS?

LUMAKRAS is a prescription medicine used to treat adults with non-small cell lung cancer (NSCLC):

- that has spread to other parts of the body or cannot be removed by surgery, **and**
- whose tumor has an abnormal KRAS G12C gene, **and**
- who have received at least one prior treatment for their cancer.

Your healthcare provider will perform a test to make sure that LUMAKRAS is right for you.

It is not known if LUMAKRAS is safe and effective in children.

What should I tell my healthcare provider before taking LUMAKRAS?

Before taking LUMAKRAS, tell your healthcare provider about all your medical conditions, including if you:

- have liver problems.
- have lung or breathing problems other than lung cancer.
- are pregnant or plan to become pregnant. It is not known if LUMAKRAS will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if LUMAKRAS passes into your breast milk. Do not breastfeed during treatment with LUMAKRAS and for 1 week after the last dose.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, dietary, and herbal supplements. LUMAKRAS can affect the way some other medicines work and some other medicines can affect the way LUMAKRAS works.

Especially tell your healthcare provider if you take antacid medicines, including Proton Pump Inhibitor (PPI) medicines or H_2 blockers during treatment with LUMAKRAS. Ask your healthcare provider if you are not sure.

How should I take LUMAKRAS?

- Take LUMAKRAS exactly as your healthcare provider tells you to take it. Do not change your dose or stop taking LUMAKRAS unless your healthcare provider tells you to.
- Take your prescribed dose of LUMAKRAS 1 time each day, at about the same time each day.
- Take LUMAKRAS with or without food.
- Swallow LUMAKRAS tablets whole. Do not chew, crush, or split tablets.
- If you cannot swallow LUMAKRAS tablets whole:
  - Place your prescribed dose of LUMAKRAS in a glass of 4 ounces (120 mL) of non-carbonated, room temperature water without crushing the tablets. Do not use any other liquids.
  - Stir or swirl the cup for about 3 minutes until the tablets are in small pieces (the tablets will not completely dissolve). The color of the mixture may be pale yellow to bright yellow.
  - Drink the LUMAKRAS and water mixture right away or within 2 hours of preparing. Do not chew pieces of the tablet.
  - Rinse the glass with an additional 4 ounces (120 mL) of water and drink to make sure that you have taken the full dose of LUMAKRAS.
  - If you do not drink the mixture right away, stir or swirl the mixture again before drinking.
- If you take an antacid medicine, take LUMAKRAS either 4 hours before or 10 hours after the antacid.
- If you miss a dose of LUMAKRAS, take the dose as soon as you remember. If it has been more than 6 hours, do not take the dose. Take your next dose at your regularly scheduled time the next day. Do not take 2 doses at the same time to make up for a missed dose.
- If you vomit after taking a dose of LUMAKRAS, do not take an extra dose. Take your next dose at your regularly scheduled time the next day.

What are possible side effects of LUMAKRAS?

LUMAKRAS may cause serious side effects, including:

- **Liver problems.** LUMAKRAS may cause abnormal liver blood test results. Your healthcare provider should do blood tests before starting and during treatment with LUMAKRAS to check your liver function. Tell your healthcare provider right away if you get any signs or symptoms of liver problems, including:
  - your skin or the white part of your eyes turns yellow (jaundice)
  - dark or "tea-colored" urine
  - light-colored stools (bowel movements)
  - tiredness or weakness
  - nausea or vomiting
  - bleeding or bruising
  - loss of appetite
  - pain, aching, or tenderness on the right side of your stomach-area (abdomen)

- **Lung or breathing problems.** LUMAKRAS may cause inflammation of the lungs that can lead to death. Tell your healthcare provider or get emergency medical help right away if you have new or worsening shortness of breath, cough, or fever.

Your healthcare provider may change your dose, temporarily stop, or permanently stop treatment with LUMAKRAS if you develop side effects.

The most common side effects of LUMAKRAS include:

- diarrhea
- muscle or bone pain
- nausea
- tiredness
- liver problems
- cough
- changes in liver function tests
- changes in certain other blood tests

These are not all the possible side effects of LUMAKRAS.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.
You may also report side effects to Amgen at 1-800-772-6436 (1-800-77-AMGEN).

How should I store LUMAKRAS?

- Store LUMAKRAS at room temperature between 68°F to 77°F (20°C to 25°C).
- The bottle has a child-resistant closure.

Keep LUMAKRAS and all medicines out of the reach of children.

General information about the safe and effective use of LUMAKRAS.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use LUMAKRAS for a condition for which it was not prescribed. Do not give LUMAKRAS to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about LUMAKRAS that is written for healthcare professionals.

What are the ingredients in LUMAKRAS?

Active Ingredient: sotorasib
Inactive Ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. Tablet film coating material contains polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow and iron oxide red (320 mg tablet only).

AMGEN®

Manufactured by: Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799 U.S.A

For more information, go to www.LUMAKRAS.com or call 1-800-772-6436 (1-800-77-AMGEN).
This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 01/2023
[part number] v2