Summary Report of Benefit-Risk Assessment

LUMAKRAS FILM-COATED TABLET 120 MG

NEW DRUG APPLICATION

Active Ingredient(s)	Sotorasib
Product Registrant	Amgen Biotechnology Singapore Pte Ltd
Product Registration Number	SIN16522P
Application Route	Abridged evaluation
Date of Approval	28 June 2022

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A INTRODUCTION

Lumakras is indicated for the 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 systemic therapy.

The active substance, sotorasib, is an inhibitor of the RAS GTPase family. It binds irreversibly to KRAS G12C, thereby locking the kinase receptor in an inactive conformation. Inactivation of KRAS G12C by sotorasib blocks tumour cell signalling and survival, inhibits cell growth, and promotes apoptosis selectively in tumours harbouring KRAS G12C.

Lumakras is available as a film-coated tablet containing 120 mg of sotorasib. Other ingredients in the tablet core are microcrystalline cellulose, lactose monohydrate, croscarmellose sodium and magnesium stearate. Ingredients in the film coat include polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and iron oxide yellow.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, sotorasib, is manufactured at SAFC Inc., Verona, USA and AMPAC Fine Chemicals LLC, Rancho Cordova, USA. The drug product, Lumakras Film-Coated Tablet 120mg, is manufactured at Patheon Inc., Mississauga, Canada.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented was adequate to support storage at or below 30^{o}C with a re-test period of 24 months. The packaging is double low density polyethylene bags within a high-density polyethylene (HDPE) drum, and each bag is sealed with cable ties. The HDPE drum is then sealed with a HDPE lid.

Drug product:

The tablet is manufactured using a dry granulation approach, followed by film-coating. The process is considered to be a standard process.

The manufacturing site involved is compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the

manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support a shelf-life of 24 months when stored at or below 30ºC. The tablets are presented in either high density polyethylene (HDPE) bottles containing 120 tablets, or in PVC/PE/PVDC-Alu or PVC/Aclar-Alu blisters containing 8 tablets. The shelf-life after opening of the HDPE bottle is 60 days and is supported with appropriate data.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of sotorasib in the treatment of KRAS G12C-mutated locally advanced or metastatic NSCLC was based on one pivotal Phase 1/2, ongoing, open-label, non-randomised study (Study 20170543) in subjects with KRAS G12C-mutated advanced solid tumours. The Phase 2 NSCLC group provided the key data for clinical efficacy, where subjects with KRAS G12C-mutated locally advanced and metastatic NSCLC were treated with sotorasib monotherapy at 960 mg once daily until disease progression or unacceptable toxicity.

Subjects were required to have prospectively identified KRAS G12C-mutated NSCLC in tumour tissue samples using the Qiagen *therascreen*® KRAS RGQ polymerase chain reaction *in vitro* diagnostic assay performed in the central laboratory. Subjects must have progressed after receiving at least one and no more than three prior systemic therapies, which must include an 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).

The primary efficacy endpoint was the objective response rate (ORR), defined as confirmed complete response (CR) or confirmed partial response (PR) as measured by computed tomography (CT) or magnetic resonance imaging (MRI) and assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 criteria by blinded independent central review (BICR). Confirmation of response required CT or MRI repeat assessment at least 4 weeks after the first detection of response. Secondary efficacy endpoints included duration of response (DOR), time to response (TTR), disease control rate (DCR), progression-free survival (PFS) and overall survival (OS).

The success criteria for the primary endpoint, ORR, was considered to be met if the lower limit of the 95% confidence interval (CI) of the point estimate excluded the pre-specified benchmark rate of 23%. This benchmark ORR was selected based on the Phase 3 REVEL study where ramucirumab plus docetaxel as second-line treatment after disease progression on platinum-based therapy showed an ORR of 23% (95% CI: 20, 26). The benchmark reference was considered as a reasonable estimate for the comparison of efficacy of sotorasib with current standard of care.

The use of ORR as a primary endpoint in a single-arm uncontrolled study, although not ideal for confirmation of clinical benefit, was considered acceptable in the context of the heavily pre-

treated population who are in second to fourth lines of therapy with limited treatment alternatives. In particular, there are currently no approved targeted treatment for patients with KRAS G12C-mutated advanced NSCLC.

A total of 126 subjects with KRAS G12C-mutated locally advanced or metastatic NSCLC were enrolled in the Phase 2 portion of the study and had received at least one dose of sotorasib. Of these, 123 subjects had at least one measurable lesion (based on central review) at baseline and were included in the full analysis set for efficacy assessments.

Of the 126 subjects with NSCLC, 50.0% were male and female respectively, 81.7% were White, and 15.1% were Asian. The median age was 63.5 years (range 37 to 80 years). The majority of the subjects had non-squamous NSCLC (99.2%) and Stage IV (metastatic) disease at screening (96.0%), while 4.0% had Stage III (locally advanced) disease. Subjects had received a median of 2 prior lines of anti-cancer therapy: 54 subjects (42.9%) had received 1 prior line, 44 (34.9%) had received 2 prior lines, and 28 (22.2%) had received 3 prior lines. A total of 113 subjects (89.7%) had prior platinum-based chemotherapy, 115 subjects (91.3%) received prior anti-PD-1/PD-L1 immunotherapy, 25 subjects (19.8%) had received anti-VEGF biological therapy and 9 subjects (7.1%) had received targeted small molecule therapies. A total of 102 subjects (81.0%) had received and progressed on treatment with both anti-PD-1/PD-L1 and platinum-based chemotherapy.

Efficacy data reported for the primary analysis were based on the data cut-off date of 01 September 2020. Updated efficacy data for ORR and DOR from the 01 December 2020 data cut-off date were also provided. In the updated efficacy analysis, one additional patient was identified as being eligible to be included in the full analysis set (due to identification of a measurable target lesion on the patient's baseline imaging that had not been previously identified), hence a total of 124 patients were included in the full analysis set.

The ORR in the primary analysis was 37.4% (95% CI: 28.8, 46.6) with 2 subjects (1.6%) achieving a complete response and 44 subjects (35.8%) achieving a partial response. The primary analysis success threshold had been met, as the lower limit of the 95% CI excluded the pre-specified benchmark ORR of 23%. Among the 46 responders, the median time to response was 1.35 months (range 1.2 to 6.1). The median DOR was 8.4 months (95% CI: 6.9, 8.4). The updated efficacy analysis based on the cut-off date of 01 December 2020 showed a consistent ORR of 37.1% (95% CI: 28.6, 46.2) and median DOR of 10.0 months (95% CI: 6.9, 11.1).

Subgroup analyses (based on the updated 01 December 2020 analysis) by number of prior lines of therapies showed consistent ORR point estimates in those with one (39.6%), two (32.6%) or more than two (39.3%) prior lines of anti-cancer therapy. The ORR was also consistent in the subgroups of subjects who had received prior anti-PD-1/PD-L1 therapy (36.3%) or who did not receive such therapy (45.5%), and in those who had received prior platinum-based chemotherapy (33.3%) or did not receive such therapy (69.2%). Similarly, the ORR was consistent in the subgroup of subjects who received prior platinum-based chemotherapy and prior anti-PD1/PD-L1 therapy (32%) or those who did not receive both these prior therapies (58.3%). Based on the recruited patient population and the overall consistent subgroup analyses results, the data supported the indication for patients who had received at least one prior systemic therapy.

In the updated analysis, the median PFS based on central review was 6.8 months (95% CI: 5.1, 8.2). The median OS was 12.5 months (95% CI: 10.0, not estimable). However,

meaningful conclusions could not be drawn based on these time-to-event endpoints in the absence of a comparator arm in a single-arm study.

Summary of efficacy results

	Primary analysis (data cut-off 01 September 2020) (N=123)	Updated analysis (data cut-off 01 December 2020) (N=124)
Primary efficacy endpoint		
ORR, n (%) (95% CI)	46 (37.4%) (28.84, 46.58)	46 (37.1%) (28.60, 46.23)
Best overall response Complete response (CR) Partial response (PR) Stable disease (SD) Progressive disease (PD) Not evaluable (NE) Not done	 2 (1.6%) 44 (35.8%) 53 (43.1%) 20 (16.3%) 2 (1.6%) 2 (1.6%)	 3 (2.4%) 43 (34.7%) 54 (43.5%) 20 (16.1%) 2 (1.6%) 2 (1.6%)
Secondary efficacy endpoints		
DCR, n (%) (95% CI)	99 (80.5%) (72.37, 87.08)	100 (80.6%) (72.58, 87.19)
DOR (months) Median (95% CI)	 8.4 (6.9, 8.4)	 10.0 (6.9, 11.1)
TTR (months) Median Min, Max	 1.35 1.2, 6.1	 1.35 1.2, 10.1
PFS (months) Median (95% CI)	 6.7 (4.9, 8.1)	 6.8 (5.1, 8.2)
OS (months) Median (95% CI)	 12.0 (9.5, NE)	 12.5 (10.0, NE)

NE = not estimable

Overall, the ORR observed with sotorasib was considered clinically relevant and compared favourably with that of other approved second-line therapies in a similar patient population with previously treated advanced NSCLC, where reported ORRs ranged from 5 to 23%.

In order to further contextualise the results from the single-arm study, the applicant has conducted three real-world evidence studies, which showed that outcomes in second or later lines of therapy for patients with KRAS G12C-mutated advanced NSCLC were as poor as the overall patient population with advanced NSCLC. The median OS (12.5 months) and PFS (6.8 months) with sotorasib in patients in second to fourth lines of therapy in the Phase 2 single-arm study appeared promising when compared to the real-world evidence studies (OS 3.0 to 10.2 months; PFS 1.8 to 4.0 months). However, such cross-study comparisons should be interpreted with caution for such time-to-event endpoints. In the absence of a comparator arm in a single-arm study, meaningful conclusions cannot be drawn based on the PFS and OS results. The treatment benefit in terms of survival outcomes will need to be confirmed in the ongoing Phase 3, randomised, open-label study (Study 20190009), which will evaluate sotorasib versus docetaxel in previously treated KRAS G12C-mutated, locally advanced unresectable or metastatic NSCLC.

D ASSESSMENT OF CLINICAL SAFETY

The analysis of the safety profile of sotorasib is primarily based on the pooled data from subjects with NSCLC who were treated with sotorasib monotherapy at 960 mg once daily (i.e., the intended dose) from the Phase 1 and Phase 2 portions of Study 20170543. The data cut-off dates for the safety analyses were 06 July 2020 for the Phase 1 portion and 01 September 2020 for the Phase 2 portion. In addition, a 90-day Safety Update was provided based on the data cut-off date of 01 December 2020, which formed the key dataset for evaluating the safety of sotorasib 960 mg administered as a once daily dose.

Safety data of sotorasib monotherapy in subjects who had received the intended dose for all tumour types (NSCLC, colorectal cancer, etc) and in the total population who had received sotorasib monotherapy at any dose for all tumour types in Study 20170543 were also provided as a comparison.

Based on the 01 December 2020 data cut-off for Study 20170543, the safety population comprised a total of 214 subjects with NSCLC who had received at least one dose of sotorasib monotherapy at 960 mg once daily. Subjects were treated with sotorasib for a median of 23.79 weeks, with 45.8% of subjects receiving treatment for at least 6 months and 9.3% for at least 12 months.

Summary of treatment-emergent adverse events (AEs) in Study 20170543 (safety analysis set)

	960 mg Once Daily		Any Dose/Tumour Type
	NSCLC (N=214)	Any Tumour Type (N=377)	Total Population (N=456)
Any AE	211 (98.6%)	364 (96.6%)	441 (96.7%)
Treatment-related AE	146 (68.2%)	220 (58.4%)	270 (59.2%)
Grade ≥3 AE	128 (59.8%)	197 (52.3%)	243 (53.3%)
Serious AE (SAE)	110 (51.4%)	173 (45.9%)	206 (45.2%)
AE leading to treatment discontinuation	19 (8.9%)	23 (6.1%)	28 (6.1%)
Fatal AE	38 (17.8%)	59 (15.6%)	72 (15.8%)
Treatment-related fatal AE	0	0	0

Treatment-emergent adverse events (AEs) were reported for 211/214 subjects (98.6%) with NSCLC. The most frequently reported AEs were diarrhoea (43.0%), nausea (26.6%), fatigue (24.3%), increased AST (19.6%), increased ALT (19.2%), arthralgia (19.2%), back pain (18.2%), vomiting (17.3%), constipation (16.8%), dyspnoea (15.4%), anaemia (13.6%), cough (13.6%), increased blood alkaline phosphatase (ALP) (13.1%), decreased appetite (12.1%), headache (12.1%), peripheral oedema (12.1%), abdominal pain (11.2%), and pneumonia (10.7%). Treatment-related AEs were reported for 146/214 subjects (68.2%), the most frequently reported being diarrhoea (28.0%), increased ALT (15.4%), increased AST (15.4%), nausea (15.0%), and fatigue (11.2%).

Grade ≥3 AEs were reported in 128/214 subjects (59.8%), the most frequently reported being increased ALT (7.5%), pneumonia (7.0%), increased AST (6.5%), pleural effusion (5.6%), and diarrhoea (5.1%). Treatment-related Grade ≥3 AEs were reported for 43 subjects (20.1%), and the most frequently reported were increased ALT (7.0%), increased AST (5.6%), and diarrhoea (3.7%).

Serious AEs (SAEs) were reported for 110/214 subjects (51.4%). The most frequently reported SAEs were pneumonia (7.5%), NSCLC (4.7%), pleural effusion (3.7%), respiratory failure (3.7%), back pain (2.8%), and dyspnoea (2.3%). AEs leading to discontinuation of sotorasib were reported for 19 subjects (8.9%). The most frequently reported AEs leading to discontinuation were increased ALT (1.9%), increased AST (1.9%), and drug-induced liver

injury (1.4%). Fatal AEs were reported for 38 subjects (17.8%), none of which were assessed by the investigator as related to study treatment.

Hepatotoxicity was one of the main AEs of concern for sotorasib reported in 61/214 subjects (28.5%), comprising mainly AEs involving liver enzyme abnormalities (increased AST, increased ALT, increased blood ALP). Serious hepatotoxicity AEs were reported for 9/214 subjects (4.2%). There were 26/214 subjects (12.1%) and 10/214 subjects (4.7%) who reported hepatotoxicity AEs leading to dose modification and discontinuation of sotorasib, respectively. None of the hepatotoxicity events met Hy's law criteria, and there were no cases of liver failure or fatal cases. The median time to first onset of any grade hepatotoxicity AEs was 43.0 days (range 1 to 295 days). The majority of the hepatotoxicity events resolved with a median duration of 46.0 days (range 22 to 85 days). The hepatotoxicity risks have been adequately described in the proposed package insert, including recommendations for dose reduction, interruption and discontinuation.

Events of interstitial lung disease (ILD)/pneumonitis were reported at an incidence of 1.4% (3/214 subjects). All cases were Grade 3 or 4 and the median time to first onset for ILD/pneumonitis was 2 weeks (range 2 to 18 weeks). Nonetheless, the events were confounded by NSCLC disease progression and the use of prior therapies that are known to be associated with pneumonitis such as immune checkpoint inhibitors. Given that pneumonitis is a serious and potentially fatal event, warnings on ILD/pneumonitis including dose modification guidelines have been included in the proposed package insert, which is acceptable.

Overall, the safety profile of sotorasib was considered acceptable in the context of the treatment for a life-threatening disease. The main safety risks, including hepatotoxicity and ILD/pneumonitis, have been adequately described in the package insert and can be managed with monitoring and dose modifications.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Advanced NSCLC is a serious and life-threatening disease with a 5-year survival rate of 5.2%. Locally advanced or metastatic NSCLC with KRAS G12C mutation is a genetically distinct form of lung cancer that is not curable with available therapies. Standard of care therapies for patients with KRAS G12C-mutated advanced NSCLC currently includes the same treatments for advanced NSCLC that does not harbour the KRAS G12C mutation. There are currently no approved targeted therapies specifically for patients with KRAS G12C-mutated advanced NSCLC. Hence, there is a medical need for new biomarker-driven anticancer therapies in this patient population.

The efficacy of sotorasib in the treatment of previously treated patients with KRAS G12C-mutated locally advanced or metastatic NSCLC has been demonstrated in Study 20170543 based on an ORR of 37.4% (95% CI: 28.8, 46.6) at the initial data cut-off date (01 September 2020), which was maintained at the updated data cut-off date (01 December 2020) with an ORR of 37.1% (95% CI: 28.6, 46.2). The updated median DOR was 10.0 months (95% CI: 6.9, 11.1). The ORR results compared favourably with that of historical controls in a similar patient population (ORR 5% to 23%). The magnitude of the response could be considered clinically meaningful in the context of the patient population who had received one to three prior lines of therapies, including anti-PD-1/PD-L1 and/or platinum-based therapies, and who have limited treatment options.

The updated median PFS was 6.8 months (95% CI: 5.1, 8.2) and median OS was 12.5 months (95% CI: 10.0, not estimable). However, meaningful conclusions could not be drawn based on these time-to-event endpoints in the absence of a comparator arm in a single-arm study. The treatment benefit of sotorasib in terms of survival outcomes will need to be confirmed in the ongoing Phase 3, randomised, active-controlled study (Study 20190009).

The most commonly reported AEs with sotorasib comprised mainly gastrointestinal AEs (diarrhoea [43.0%], nausea [26.6%], vomiting [17.3%], constipation [16.8%], abdominal pain [11.2%]), liver enzyme abnormalities (increased AST [19.6%] and ALT [19.2%]), fatigue (24.3%), arthralgia (19.2%), back pain (18.2%), dyspnoea (15.4%), anaemia (13.6%), cough (13.6%), increased blood alkaline phosphatase (ALP) (13.1%), decreased appetite (12.1%), headache (12.1%), peripheral oedema (12.1%), and pneumonia (10.7%).

The main safety risks identified with sotorasib were hepatotoxicity and ILD/pneumonitis. Hepatotoxicity was characterised by increases in ALT or AST, with 4.2% of hepatotoxicity AEs reported as serious. There were no fatalities related to hepatotoxicity. ILD/pneumonitis occurred at an incidence of 1.4%, but the cases were confounded by NSCLC disease progression and use of prior therapies known to cause pneumonitis. These safety concerns have been adequately addressed by warnings and dose modification recommendations in the package insert.

Overall, the ORR observed with sotorasib together with the durability of the responses were considered clinically meaningful and the safety profile was acceptable in the target patient population who have received at least one prior systemic therapy. Taken together, the benefit-risk profile of sotorasib in the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits have been demonstrated to outweigh the risks of Lumakras for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy, and approval of the product registration was granted on 28 June 2022.

APPROVED PACKAGE INSERT AT REGISTRATION

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), who have received at least one prior systemic therapy.

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.

2.2 Recommended Dosage and Administration

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

Take 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 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 (4 tablets) once daily
Second dose reduction	240 mg (2 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: 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 (%)	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, 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

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

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

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

Coadministration of LUMAKRAS with a P-gp substrate (digoxin) increased digoxin plasma concentrations *[see Clinical Pharmacology (12.3)]*, which may increase the adverse reactions of digoxin. 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.

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)*.

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.

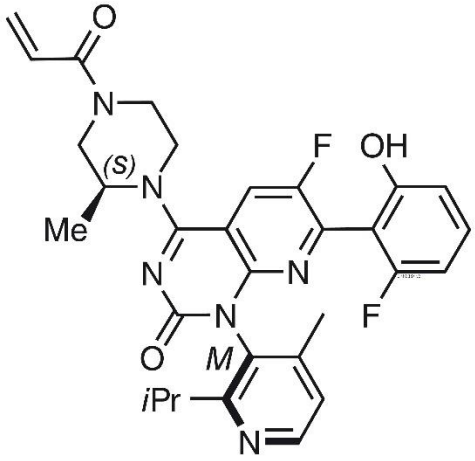
8.5 Geriatric Use

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 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, and iron oxide yellow.

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.

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.

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) 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:

- Two HDPE bottles with child-resistant polypropylene closures and aluminum foil induction seal liners. Each HDPE bottle contains 120 film-coated tablets.
- Thirty PVC/PVDC blisters with aluminum foil backing in each carton. Each blister card contains 8 film-coated tablets.
- Thirty PVC/Aclar blisters with aluminum foil backing in each carton. Each blister card contains 8 film-coated tablets.

Not all presentations may be marketed.

Storage and Handling

Store below 30°C.

HDPE bottle
Shelf-life after first opening: 60 days.

17 PATIENT COUNSELING 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)]*.

Product Owner :
Amgen Inc.

One Amgen Center Drive
Thousand Oaks, CA 91320-1799 U.S.A.

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