

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214665Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214665
PDUFA Goal Date	August 16, 2021
OSE RCM #	2020-1337
Reviewer Name	Mei-Yean Chen, Pharm.D.
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Division Deputy Director	Doris Auth, Pharm.D.
Review Completion Date	May 17, 2021
Subject	Evaluation of Need for a REMS
Established Name	Sotorasib
Trade Name	Lumakras
Name of Applicant	Amgen
Therapeutic Class	a RAS GTPase inhibitor
Formulation(s)	120 mg oral tablet
Dosing Regimen	960 mg (eight 120 mg tablet) orally once daily

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity sotorasib is necessary to ensure the benefits outweigh its risks. Amgen, Inc. submitted a New Drug Application (NDA) 214665 for sotorasib with the proposed indication for the treatment of adult patients with Kirsten rat sarcoma (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. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). The risks associated with sotorasib are hepatotoxicity and interstitial lung disease/pneumonitis. The applicant did not submit a proposed REMS or risk management plan with this application.

The Division of Risk Management (DRM) and the Division of Oncology 2 (DO2) have agreed that a REMS is not needed to ensure the benefits of sotorasib outweigh its risks. Patients with KRAS G12C-mutated locally advanced or metastatic NSCLC currently have no targeted therapy and there is an unmet medical need for this population. The clinical trial of sotorasib demonstrated an overall response rate (ORR) of 36% in patients who have received at least one prior systemic therapy. Sotorasib will be the first targeted therapy for patients with KRAS G12C mutated NSCLC. The risk of hepatotoxicity and interstitial lung disease/pneumonitis associated with sotorasib will be described in Warnings and Precautions of the prescribing information. At the time of this review, none of these risks warrants a boxed warning. The clinicians, typically oncologists, who will prescribe sotorasib are familiar by their experience and training with the management of these toxicities without additional risk mitigation measures beyond labeling.

1 Introduction

This review evaluates whether a REMS for the new molecular entity (NME)^a sotorasib is necessary to ensure the benefits outweigh its risks. Amgen, Inc. submitted a New Drug Application (NDA) 214665 for sotorasib with the proposed indication for the treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, as determined by an FDA-approved test, who have received at least one prior systemic therapy. This indication is approved under accelerated approval based on 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). This application is under review in the DO2. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Sotorasib is a rat sarcoma (RAS) guanosine triphosphatases (GTPases) inhibitor that targets KRAS G12C by covalently binding to the unique cysteine of KRAS G12C, locking the protein in an inactive state that

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

prevents downstream signaling without affecting wild-type KRAS. Sotorasib reduces tumor cell signaling, inhibits cell growth, and promotes apoptosis in a subset of tumors harboring KRAS G12C. Sotorasib will be supplied as 120 mg oral tablet. The recommended dose of sotorasib is 960 mg (eight tablets) orally once daily until disease progression or unacceptable toxicity.^b Sotorasib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 214665 relevant to this review:

- 06/01/2018: Investigation New Drug (IND) 139023 for advanced solid tumors with a specific KRAS mutation was submitted.
- 05/01/2019: Orphan drug designation granted for treatment of KRAS p.G12C mutated NSCLS.
- 08/05/2020: Fast track designation granted.
- 12/16/2020: NDA 214665 submitted.
- 03/11/2021: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that there were no safety signals at this time for which a REMS is currently being considered.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Lung cancer is the leading cause of cancer death in men and the second leading cause of cancer death in women globally, with estimated 2.1 million new cases and 1.8 million deaths worldwide for 2018. In the United States (US) in 2020, there were about 228,000 new cases of lung cancer and more than 135,000 deaths from lung cancer^{b,1} NSCLC accounts for 85% of globally diagnosed lung cancer cases. Most newly diagnosed NSCLC patients have advanced disease. If not treated, NSCLC is fatal in most patients within one year or less.^c The five-year survival rate of advanced NSCLC (stage IIIB and IV) is about 5.2%.

Several proto-oncogene mutations have been implicated in the development of NSCLC. Mutations in the RAS family of proto-oncogenes are the most prevalent among these mutations, which consists of three closely related genes (HRAS, KRAS, and NRAS) that encode GTPases responsible for regulating cellular proliferation and survival. KRAS is the most frequently mutated isoform in most cancers and an estimated 80% KRAS mutation occur at codon 12. The KRAS p.G12C mutation in codon 12 is a glycine to cysteine substitution at amino acid position 12. This results in accumulation of guanosine triphosphate (GTP)-bound KRAS leads to proliferative and survival signaling in tumor cells. Approximately 13% of NSCLC cases in North America and Europe regions², and approximately 3% of

^b Section 505-1 (a) of the FD&C Act: FDAAA factor (A): *The estimated size of the population likely to use the drug involved.*

^c Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

NSCLC cases in Asia have been identified to have the KRAS p.G12C mutation.³ This mutation is associated with a history of smoking tobacco, higher programmed death-ligand 1 (PD-L1) expression and tumor mutational burden than wild-type NSCLC cells.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The National Comprehensive Cancer Network (NCCN) guidelines call for testing of all patients with NSCLC for oncogenic driver mutations.⁴ Patients whose tumors have actionable mutations, such as mutations of epidermal growth factor receptor (EGFR) gene, anaplastic lymphoma kinase (ALK) gene, B-raf (BRAF) gene, proto-oncogene tyrosine-protein kinase ROS (ROS1), or neurotrophic tyrosine kinase (NTRK) gene may receive target therapies directed at these specific oncogenic drivers in first or later lines. RAS targeting has proven challenging owing to multiple mutation subgroupings, difficulty targeting specific binding pockets, and a multiplicity of targets. The role of KRAS mutations in human cancers has been known for decades, but no anticancer therapies that specifically target KRAS G12C mutation are currently approved for the treatment of patients with NSCLC. Further, KRAS mutations rarely occur concomitantly with other oncogenic mutations. Most patients with KRAS mutations are not candidates for currently approved targeted therapies and are typically treated as patients without targetable mutations, such as chemotherapy, immunotherapy, or antiangiogenic agents.

In first line therapy, patients with KRAS G12C mutated NSCLC are typically treated with platinum-based chemotherapy with or without an immune checkpoint inhibitor. Second line available therapies for this population include immune checkpoint inhibitors and pemetrexed if not already given up front, docetaxel with ramucirumab, or docetaxel alone.

4 Benefit Assessment

A single-arm, open-label, multicenter trial (CodeBreak 100, [NCT03600883]) demonstrated the efficacy of sotorasib in a subset of patients with locally advanced or metastatic KRAS G12C mutated NSCLC. The criteria for patients to enroll in the trial are 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 the tumor tissue samples by using the QIAGEN *therascreen* KRAS RGQ PCR Kit performed in a central laboratory. A total of 124 patients had at least one measurable lesion at baseline assessed by a Blinded Independent Review Committee (BIRC) according to RECIST v1.1 and were treated with sotorasib 960 mg once daily until disease progression or unacceptable toxicity^d.

The major efficacy outcome measure was confirmed ORR and DoR by BIRC according to RECIST v1.1.⁵ The median age of enrolled patients was 64 years (range 37 to 80 years) 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; 82% former smokers, 12% current smokers, 5% never smokers. All

^d Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

patients received at least one prior line of systemic therapy for metastatic NSCLS. Table 1 below demonstrates efficacy results in the CodeBreak 100 study.

Table 1 Efficacy results for patients with KRAS G12C mutated NSCLC who received sotorasib in CodeBreak 100

Efficacy parameter	Sotorasib, n=124
ORR, (95% confidence interval)	36 (28, 45)
Complete response rate %	2
Partial response rate %	35
DoR	
Median, months (range)	10.0 (1.3, 11.1)
Patients with duration \geq 6 months, %	58%

5 Risk Assessment & Safe-Use Conditions

The safety of sotorasib was evaluated in a pooled safety population that reflect exposure to sotorasib as a single agent at 960 mg orally once daily in 357 patients with NSCLC and other solid tumors with KRAS G12C mutation. There were 13 fatal adverse events (AEs), four due to respiratory failures, two due to cardiac arrest, and one death due to cardiac failure, gastric ulcer, large intestinal obstruction, systemic inflammatory response syndrome, pneumonia, intracranial hemorrhage, and hypovolemic shock.⁶

All risks^e associated with sotorasib listed below are currently included in the draft labeling⁵ Section 5 Warnings and Precautions.

5.1 HEPATOTOXICITY

Sotorasib can cause hepatotoxicity, which may lead to drug-induced liver injury and hepatitis. In CodeBreak 100 study, hepatotoxicity occurred in 1.7% (all grades) and 1.4% (grade 3) of patients who received sotorasib. Increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST) occurred in 18% of patients, 6% were grade 3 and 0.6% were grade 4. The median time to first onset of

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

increased ALT/AST was 9 weeks (range: 0.3 to 42 weeks). Dose interruption or reduction occurred in 7% of patient and 2.0% was discontinued due to increased ALT/AST.

If sotorasib is approved, healthcare providers (HCPs) will be advised to monitor liver function tests prior to the initiation of sotorasib, every three weeks for the first three months, then once a month or as clinically indicated. HCPs will be also advised to withhold, reduce the dose, or permanently discontinue sotorasib based on the severity of hepatotoxicity.

5.2 INTERSTITIAL LUNG DISEASE/PNEUMONITIS

Interstitial lung disease (ILD)/pneumonitis occurred in patients treated with sotorasib with prior exposure to immunotherapy or radiotherapy. In CodeBreak 100 study, ILD/pneumonitis occurred in 0.8% of patients, all cases were grade 3 or 4. The median time to first onset for ILD/pneumonitis was two weeks (range: 2 to 18 weeks). Sotorasib was discontinued due to ILD/pneumonitis in 0.6% of patients.

If approved, HCPs will be advised to monitor patients for new or worsening pulmonary symptoms indicative of ILD/pneumonitis. The labeling will advise HCPs to withhold sotorasib immediately in patients with suspected ILD/pneumonitis and discontinue sotorasib permanently if no other potential causes of ILD/pneumonitis are identified.

6 Expected Postmarket Use

If approved, it is expected that oncologists will be the likely health care providers to prescribe sotorasib, in both inpatient and outpatient settings.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for sotorasib beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of sotorasib on the basis of the efficacy and safety information currently available. The clinical reviewer's preliminary findings are that the application is appropriate for accelerated approval and the risks of hepatotoxicity and ILD/pneumonitis will be communicated in Warnings and Precautions. The clinical reviewers believe that these risks are manageable with dose interruption and the events can be appropriately handled with labeling alone.

Patients with KRAS G12C-mutated locally advanced or metastatic NSCLC currently have no targeted therapy and there is an unmet medical need for this population. The clinical trial of sotorasib demonstrated an ORR 36% in patients who have received at least one prior systemic therapy. Sotorasib will be the first targeted therapy for patients with KRAS G12C mutated NSCLC.

This reviewer recommends that, if sotorasib is approved, a REMS is not necessary to ensure its benefits outweigh its risks. The risks of hepatotoxicity and ILD/pneumonitis will be adequately described in the labeling. At the time of this review, none of these risks warrants a boxed warning. The clinicians, typically oncologists, who will prescribe sotorasib are familiar by their experience and training in the management of these toxicities without additional risk mitigation measures beyond labeling.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, DRM and DO2 agree that a REMS is not necessary for sotorasib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling were ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 REFERENCES

¹ American Cancer Society. Key statistics for Lung Cancer. www.cancer.org/cancer/lung-cancer/about/key-statistics.html. Accessed 03/24/2021

² Biernacka A, Tsongalis PD, Peterson JD, et al. The potential utility of re-mining results of somatic mutation testing: KRAS status in lung adenocarcinoma. *Cancer Genet.* 2016;209(5):195-198.

³ Liu S-Y, Sun H, Zhou J-Y, et al. Clinical characteristics and prognostic value of the KRAS G12C mutation in Chinese non-small cell lung cancer patients. *Biomark Res.* 2020;8:22.

⁴ Ettinger et al, National Comprehensive Cancer Network (NCCN) Guidelines Version 4.2021 Non-small cell lung cancer, principles of molecular and biomarker analysis, www.nccn.org, accessed 03/26/2021

⁵ Sotorasib NDA 214665 draft prescribing information, accessed 04/29/2021

⁶ Nakajima E. & Drezner N. Sotorasib NDA 214665 midcycle presentation, 03/01/2021

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