NEW DRUG APPROVAL

Brand Name	Lumakras™
Generic Name	sotorasib
Drug Manufacturer	Amgen Inc.

New Drug Approval

FDA Approval Date: May 28, 2021
Review Designation: Priority; Orphan
Type of Review: Type 1 - New Molecular Entity; New Drug Application (NDA): 214665
Dispensing Restrictions: Specialty Pharmacy Required; Limited Distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Non small-cell lung cancer (NCSLC) is the most common type of lung cancer. Like all cancers, NSCLC begins at the cellular level and causes abnormal cells in the lungs to reproduce rapidly and out of control. NSCLCs are carcinomas, which are cancers of the cells lining the surface of the lung airways. These include the bronchi, bronchioles, and alveoli.

There are three primary types of NSCLC, categorized by the type of cells affected by cancer:

- Adenocarcinoma represents 40 percent of all NSCLC diagnoses. Adenocarcinoma affects both smokers and nonsmokers. Adenocarcinoma usually begins in the outer areas of the lung, in mucus-producing cells that line the small airways, called bronchioles. Adenocarcinoma tends to grow more slowly than other types of lung cancer, which can help lead to a better prognosis.
- Squamous cell carcinoma, also called epidermoid carcinoma, is the second most common type of NSCLC, representing 25 to 30 percent of all NSCLC diagnoses. Squamous cells, thin flat cells lining the surfaces of organs, are found in the lining of the bronchi. These cancers are more likely to spread to other areas of the body, making them more difficult to treat. Squamous cell carcinoma is more closely associated with smoking than any other type of lung cancer.
- Large cell carcinoma is a rare form of NSCLC, accounting for only 10 to 15 percent of all diagnoses. It can occur anywhere in the lung and tends to be aggressive.

In 2021, there will be an estimated 236,000 cases of lung cancer in the United States. NSCLC is the most common type of lung cancer, accounting for 84% of all lung cancer diagnoses. *KRAS G12C* mutations occur in about 13% (approximately 25,000) of patients with NSCLC and in 1%-3% of colorectal and other cancers.

Efficacy

Table 1. CodeBreaK 100 (NCT03600883): Study Design Summary	
Study Population	• 124 evaluable adult patients with locally advanced or metastatic *KRAS G12C*–mutated NSCLC with disease progression after receiving an immune checkpoint inhibitor and/or platinum-based chemotherapy, an ECOG PS of 0 or 1, and at least 1 measurable lesion as defined by RECIST v1.1. • Median age: 64 years (range: 37–80 years) ○ 48% ≥65 years of age ○ 8% ≥75 years of age ○ 50% female ○ 82% White o 15% Asian ○ 2% Black ○ 70% ECOG PS 1 • 96% had stage IV disease; 99% with nonsquamous 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 • **Exclusion criteria**: ○ Active brain metastases from non-brain tumors ○ Myocardial infarction within 6 months of study Day 1 ○ GI tract disease causing inability to take oral medication
Interventions	Sotorasib was given orally at 960 mg once daily to eligible patients who had advanced NSCLC harboring the *KRAS* p.G12C mutation and received prior standard therapies.
Endpoints	• **Primary:** ORR and DOR as evaluated by BICR according to RECIST v1.1 • **Secondary:** PFS, overall survival, and safety
Safety Results	• ORR: 36% • Of those who responded to treatment, 58% had a DOR of 6 months or longer

Abbreviations: BICR, Blinded Independent Central Review; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GI, gastrointestinal; NSCLC, non–small cell lung cancer; ORR: objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Efficacy results in patients with *KRAS G12C*–mutated NSCLC in the CodeBreaK 100 study.

Table 2. Efficacy Results for CodeBreaK 100 Trial

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%

Abbreviations: 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.

Safety

ADVERSE EVENTS

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.

WARNINGS & 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.
- **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.

CONTRAINDICATIONS

None.

Clinical Pharmacology

MECHANISMS OF ACTION

Sotorasib is an inhibitor of *KRASG12C*, a tumor-restricted, mutant-oncogenic form of the RAS GTPase, KRAS. Sotorasib forms an irreversible, covalent bond with the unique cysteine of *KRASG12C*, 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 *KRASG12C* in vitro and in vivo with minimal detectable off-target activity. In mouse tumor xenograft models

sotorasib-treatment led to tumor regressions and prolonged survival and was associated with anti-tumor immunity in *KRAS G12C* models.

Dose & Administration

ADULTS

960 mg orally once daily.
Swallow tablets whole with or without food.

PEDIATRICS

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

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed. The effect of severe renal impairment (CrCl less than 30 mL/min/1.73 m2) on the pharmacokinetics of sotorasib has not been studied.

HEPATIC IMPAIRMENT

Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed. The effect of moderate to severe hepatic impairment (AST/ALT 2.5 times the upper limit of normal [ULN] or higher; or total bilirubin 1.5 times ULN or higher) on the pharmacokinetics of sotorasib has not been studied.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 120 mg.