PDL DRUG REVIEW

Proprietary Name: Lumakras®
Common Name: sotorasib
PDL Category: Antineoplastics

Summary

Pharmacology/Usage: Sotorasib, the active ingredient of Lumakras®, 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. In animal models, sotorasib treatment led to tumor regressions and prolonged survival.

Indication: 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. 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).

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women. In animal studies, use did not cause adverse developmental effects or embryo-lethality at exposures up to 4.6 times the human exposure. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated, Immediate-Release Tablets: 120mg. Swallow tablets whole; do not chew, crush, or split.

Recommended Dosage: 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. 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.

The recommended dosage is 960mg (eight 120mg tablets) PO QD until disease progression or unacceptable toxicity. Take at the same time each day with or without food. If a dose 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.

If patients have difficulty swallowing solids, disperse tablets in 120ml (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 120ml of water and drink. If the mixture is not consumed immediately, stir the mixture again to ensure that tablets are dispersed.

Dose modifications may be required for adverse reactions, such as hepatotoxicity, interstitial lung disease (ILD)/pneumonitis, nausea or vomiting despite appropriate supportive care (including antiemetic therapy), diarrhea

despite appropriate supportive care (including anti-diarrheal therapy), or other adverse reactions. Refer to the prescribing information for additional information.

No clinically meaningful differences in the pharmacokinetics of sotorasib were observed based on mild and moderate renal impairment or mild hepatic impairment. The effect of severe renal impairment or moderate to severe hepatic impairment on sotorasib pharmacokinetics has not been studied.

Drug Interactions: Coadministration of Lumakras® with gastric acid-reducing agents decreased sotorasib concentrations, which may reduce the efficacy of sotorasib. Avoid coadministration of Lumakras® with proton pump inhibitors (PPIs), H2 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.

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

Coadministration of Lumakras® with a CYP3A4 substrate decreased its plasma concentrations, 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 per its prescribing information.

Coadministration of Lumakras® with a P-gp substrate (digoxin) increased digoxin plasma levels, 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 per its prescribing information.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Lumakras®) for all grades. Please note that there was no placebo data in the prescribing information to compare with.* The most frequently reported adverse events included diarrhea (42%), nausea (26%), vomiting (17%), constipation (16%), abdominal pain (15%), hepatotoxicity (25%), cough (20%), dyspnea (16%), musculoskeletal pain (35%), arthralgia (12%), fatigue (26%), edema (15%), decreased appetite (13%), pneumonia (12%), and rash (12%). Laboratory abnormalities included increased aspartate aminotransferase (39%), increased alanine aminotransferase (38%), decreased calcium (35%), increased alkaline phosphatase (33%), increased urine protein (29%), decreased sodium (28%), decreased albumin (22%), decreased lymphocytes (48%), decreased hemoglobin (43%), and increased activated partial thromboplastin time (23%).

Lumakras® can cause hepatotoxicity, which may lead to drug-induced livery injury and hepatitis. In a phase 3 study, the median time to first onset of increased ALT/AST was 9 weeks, and increased ALT/AST leading to dose interruption or reduction occurred in 7% of patients. Lumakras® was discontinued due to increased ALT/AST in 2% of patients. Monitor liver function tests (ALT, AST, and total bilirubin) prior to starting treatment, 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, reduce dose, or permanently discontinue Lumakras® based on severity of adverse reactions.

Lumakras® can cause ILD/pneumonitis that can be fatal. In a phase 3 study, 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. Immediately withhold Lumakras® in patients with suspected ILD/pneumonitis and permanently discontinue Lumakras® if no other potential causes of ILD/pneumonitis are identified.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Amgen Inc

Analysis: The safety and efficacy of Lumakras® were assessed in a subset of patients enrolled in a single-arm, open-label, multicenter study (CodeBreaK 100). 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). Of the 126 total enrolled subjects, 2 (2%) were unevaluable for efficacy analysis due to the absence of radiographically measurable lesions at baseline. A total of 124 patients had at least one measurable lesion at baseline assessed by Blinded Independent Central Review (BICR) per RECIST v1.1 and were treated with Lumakras® until disease progression or unacceptable toxicity.

At baseline, the median age of included patients was 64 years (range 37 to 80 years), with 48% ≥65 years and 8% ≥75 years. In addition, 50% were female, 82% were white, 70% had ECOG PS 1, 96% had stage IV disease, 81% were former smokers, 12% were current smokers, and 5% were 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, and 23% received 3 prior lines of therapy.

The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) as assessed by BICR per RECIST v1.1. Efficacy results can be seen in the table below, which was adapted from the prescribing information.

Efficacy parameter	Lumakras® (N=124)
Objective Response Rate (ORR)	36%
Complete response rate, %	2%
Partial response rate, %	35%
Duration of Response	
Median, months (range)	10 (1.3+, 11.1)
Patients with duration ≥6 months, %	58%

Place in Therapy: 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, 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(s) trials. In a single-arm, open-label study that included patients with locally advanced or metastatic *KRAS G12C*-mutated NSCLC, the ORR with Lumakras® was 36%.

It is recommended that Lumakras® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Lumakras [package insert]. Thousand Oaks, CA: Amgen Inc; 2021.