adagrasib (Krazati®)

EOCCO POLICY

Policy Type:PA/SP Pharmacy Coverage Policy: EOCCO265

Description

adagrasib (Krazati®) is an orally administered selective inhibitor of Kirsten Rat Sarcoma viral oncogene homologue (KRAS) and targets tumors harboring KRAS G12C mutation.

Length of Authorization

- N/A

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
adagrasib (Krazati)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation Colorectal cancer, metastatic with a KRAS G12C mutation	200 mg tablets	180 tablets/30 days

Initial Evaluation

I. **Adagrasib (Krazati)** is considered investigational when used for all conditions, including but not limited to Non-Small Cell Lung cancer (NSCLC) and colorectal cancer (CRC).

Renewal Evaluation

I. N/A

Supporting Evidence

I. Adagrasib (Krazati) is the second FDA-approved therapy under accelerated pathway for advanced or metastatic NSCLC that harbors a KRAS G12C mutation in adults patients who have received at least one prior systemic therapy. It follows sotorasib (Lumakras), which received accelerated FDA approval in this setting. Adagrasib (Krazati) was granted accelerated FDA approval in combination with cetuximab (Erbitux) for treatment of metastatic colorectal cancer harboring KRAS G12C mutation, in adults who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy in June 2024.

NSCLC

I. KRAS mutations account for up to 25% of mutations in NSCLC and are often associated with resistance to targeted therapies and generally poor patient outcomes in patients with cancer. KRAS G12C, a subset of KRAS mutations, accounts for about 13% of mutations in NSCLC.

II. Most patients with NSCLC including *KRAS*-mutated tumors are treated with systemic chemotherapy, which includes carboplatin, pemetrexed, cisplatin, and paclitaxel. Additionally,

targeted immunotherapy such as inhibitors of programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) (e.g., pembrolizumab (Keytruda), atezolizumab (Tecentriq), nivolumab (Opdivo)) are also recommended. Vascular Endothelial Growth Factor (VEGF) inhibitor ramucirumab (Cyramza) in combination with docetaxel (Taxotere) has shown success as a subsequent-line therapy in refractory disease.

III. Adagrasib (Krazati) is a subsequent-line therapy in the advanced or metastatic NSCLC, after progression on or after at least one prior systemic chemotherapy and is indicated for patients 18 years of age and older.

IV. The National Comprehensive Cancer Network (NCCN) treatment guideline for NSCLC has given adagrasib (Krazati) a Category 2A recommendation as a subsequent-line treatment for NSCLC harboring KRAS G12C mutation, after progression on or after conventional chemotherapy and/or immunotherapy.

V. The New Drug Application (NDA) for adagrasib (Krazati) for the treatment of NSCLC was based on results from a subset of participants (cohort A) in an open-label, Phase 1/2, single-arm trial (KRYSTAL-1). Patients (N=116) with KRAS G12C mutated NSCLC, who had disease progression after platinum-based chemotherapy and/ or immunotherapy received adagrasib (Krazati) 600 mg orally twice daily for a median 15.7 months. The primary efficacy outcome was Objective Response Rate (ORR). Key secondary outcomes were Progression-free Survival (PFS), duration of response (DoR), and Overall Survival (OS). Adagrasib (Krazati) showed an ORR of 42.9% (95% CI; 33.5, 52.6), which included one patient (0.9%) complete response (CR) with remainder (n= 47) exhibiting partial responses. Additionally, participants in this cohort showed DoR of 8.5 months (95% CI; 6.2, 13.8), PFS 6.5 months (95% CI; 4.7, 8.4), and OS 12.6 months (95% CI; 9.2, 19.2).

VI. Based on the data from KRYSTAL-1 trial, the quality of the evidence to support efficacy of adagrasib (Krazati) is considered low at this time. Given the lack of comparator and single-arm open-label trial design, as well as lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy remains uncertain.

VII. The safety of adagrasib (Krazati) was based on drug exposure during the clinical trial (N=116). All participants reported any grade adverse reactions (AE) with 81.9% suffering a grade ≥ 3 AE. The most common AE included diarrhea, nausea and vomiting, fatigue, dyspnea, and increased creatinine and aspartate aminotransferase (AST). Anemia, hyponatremia, and dyspnea were reported as serious (grade ≥ 3) AE. Adagrasib (Krazati) led to 82.8% dose reduction or therapy interruptions, with 15.5% of patients requiring permanent discontinuation. Twenty (17.2%) patient deaths were reported during the trial, of which, two (1.7%) were ascribed as treatment-emergent (cardiac failure and pulmonary hemorrhage). Current patient exposure to adagrasib (Krazati) is limited to clinical trial participants; thus, the real-world safety profile and patient experience with this drug remain undefined. Based on a single-arm, open-label clinical trial in a small patient population, the overall safety profile of adagrasib (Krazati) is largely unknown.

VIII. Single-arm, open-label clinical trial may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a

single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.

IX. Targeted therapies for treatment of NSCLC have garnered interest in recent years and may be considered part of a paradigm shift in the management of NSCLC based on histology and actionable driver mutations. However, while initially effective, many targeted therapies have been associated with increased drug resistance after their initial use. Acquired resistance to current molecularly targeted therapies in lung cancer presents a major clinical challenge. Additionally, targeted therapy approach is also susceptible to failure due to escape mutations.

X. Ongoing research focuses on identifying potential novel biomarkers and mechanisms involved in resistance to these therapies. In this regard, conventional chemotherapy agents (e.g., docetaxel, pemetrexed) and immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab) remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Additionally, combination regimens containing angiogenesis inhibitors with conventional chemotherapy agents (e.g., ramucirumab and docetaxel) have been successful treatment options based on a Phase 3 clinical trial reporting OS of 10.5 months versus docetaxel monotherapy 9.1 months (HR 0.86; 95% CI 0.75, 0.98; p 0.023). The efficacy and safety of targeted agents such as adagrasib (Krazati) in comparison with, or in combination with, currently established regimens, have not been studied and remain unknown.

Colorectal cancer

I. Colorectal cancer (CRC) is the third most prevalent cancer worldwide and the second most common cause of cancer death in the United States. Initial clinical presentation as mCRC occurs in approximately 20% of patients and nearly 70% of patients with localized disease eventually develop metastases. In 2023, approximately 150,000 individuals will be diagnosed with CRC and over 50,000 individuals will die from the disease. KRAS mutation presents in more than 50% of CRC cases. The KRAS glycine-to-cysteine mutation at codon 12 (KRAS G12C) occurs in up to 4% of patients and is associated with short responses to standard chemotherapy and worse overall survival (OS) compared to wildtype tumors.

II. The National Comprehensive Cancer Network (NCCN) recommends fluoropyrimidine-based regimen in combination with oxaliplatin and/or irinotecan in the first- and second-line setting. In patients with mCRC with confirmed KRAS G12C mutation, sotorasib (Lumakras) and adagrasib (Krazati) with cetuximab (Erbitux) or panitumumab (Vectibix) are recommended as second-line and subsequent therapy options (category 2A recommendation).

III. Adagrasib (Krazati) was studied in a Phase 1/2, open-label, non-randomized, single arm trial. The trial evaluated the efficacy of adagrasib (Krazati) monotherapy (n=44) and adagrasib (Krazati) in combination with IV cetuximab (Erbitux) (n=32) in a total of 76 participant 18 years and older with metastatic colorectal cancer with confirmed KRAS G12C mutation. Participants had at least one prior platinum-containing chemotherapy regiment or check point inhibitor. Participants with brain metastases or other malignancies were excluded. Baseline characteristics were similar between both cohorts, all participants had received fluoropyrimidine-based chemotherapy, majority had also received oxaliplatin, irinotecan or both, median number of previous lines of systemic therapy was three.

IV. After a median follow up of 20.1 months and 17.5 months, the primary endpoint of objective response rate (ORR) was 19% (95% CI, 8 to 33) in the monotherapy group and 46% (95% CI, 28 to 66) in the combination group. Median PFS was 5.6 months (95% CI, 4.1 to 8.3) and 6.9 months (95% CI, 5.4 to 8.1) and OS was 19.8 months (95% CI, 12.5 to 23.0) and 13.4 months (95% CI, 9.5 to 20.1), respectively.

V. Longer follow up analysis from KRYSTAL-1 presented with the 2025 Gastrointestinal Cancer Symposium demonstrated that at a median follow-up of 20.4 months (original trial's median follow-up was 20.1 months), updated data showed that the overall response rate (ORR) was 34% (95% CI, 25%-45%) in the combination group.

VI. Events that occurred in at least 20% of the patients were diarrhea (66%), nausea (57%), vomiting (45%), and fatigue (45%). Treatment related adverse events that led to dose reductions occurred in 17 patients (39%) in the monotherapy group. In the combination group, nausea (62%), diarrhea (56%), vomiting (53%), dermatitis acneiform (47%), fatigue (47%), dry skin (41%), headache (31%), dizziness (25%), maculopapular rash (25%), and stomatitis (22%) were the most common adverse events. Treatment related adverse events that led to dose reductions occurred in 10 patients (31%) and 5 patients (16%) discontinued due to treatment related adverse events.

VII. Single-arm, open-label clinical trial may provide indicators of primary efficacy. However, data from these trials are insufficient to determine causal relationship between the drug use with patient outcomes and may not be clinically meaningful to make healthcare decisions. Additionally, the primary endpoint, ORR, despite being considered an optimal marker for a single-arm study design, is not a strong surrogate marker. Overall Response Rate (ORR) is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity.

VIII. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for NSCLC note that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Despite the accelerated FDA-approval, continued approval of adagrasib (Krazati) as a subsequent-line treatment of NSCLC and mCRC, remains contingent upon verification of clinical benefit in confirmatory trials. Additionally, an expanded access program via manufacturer, as part of the ongoing clinical studies of adagrasib (Krazati), remains a practical option and an alternative path to treatment for qualifying patients.

IX. Currently, there are multiple clinical trials (Phase 1b / 2) ongoing for adagrasib (Krazati) in the settings of NSCLC, colorectal cancer, and other solid tumors harboring KRAS G12C mutation. Additionally, adagrasib (Krazati) is being studied as a combination regimen with other targeted therapies (e.g., MEK inhibitor, EGFR inhibitor, SHP2 inhibitor) for the treatment of NSCLC. These clinical trials are in early phases and as of June 2025, data is not available for review.

Investigational or Not Medically Necessary Uses

I. Adagrasib (Krazati) has not been sufficiently studied for safety and efficacy for any condition to date.

References

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6. National comprehensive Cancer Network. NCCN Guidelines: Non-small Cell Lung Cancer V3.2025. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated January 14, 2025.
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8. National comprehensive Cancer Network. NCCN Guidelines: Colon Cancer Versions 3.2025. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated April 24, 2025.
9. National comprehensive Cancer Network. NCCN Guidelines: Rectal Cancer Versions 2.2025. Available at: http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated March 31, 2025.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
regorafenib (Stivarga®)	Gastrointestinal stromal tumor, metastatic colorectal cancer, hepatocellular carcinoma
trifluridine/tipiracil (Lonsurf®)	Stomach or esophagogastric adenocarcinoma, metastatic colorectal cancer
encorafenib (Braftovi®), binimetinib (Mektovi®)	Malignant melanoma (BRAF V600E mutation), metastatic colorectal cancer with BRAF V600E mutation
fruquintinib (Fruzaqla™)	Metastatic colorectal cancer (mCRC)
sotorasib (Lumakras™)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation, Colorectal cancer, metastatic with a KRAS G12C mutation

Policy Implementation/Update

Action and Summary of Changes	Date
Added new FDA approved indication for treatment of metastatic colorectal cancer with KRAS G12C mutation to E/I section with supporting evidence. Updated related polices table. Updated QL table to reflect correct 200mg tablet.	06/2025
Policy created	11/2022