PRIOR AUTHORIZATION POLICY

POLICY: Oncology (Oral – Kirsten RAt Sarcoma Virus Inhibitor) – Krazati Prior Authorization Policy
- Krazati™ (adagrasib tablets – Mirati Therapeutics)

REVIEW DATE: 01/08/2025; selected revision 05/14/2025

INSTRUCTIONS FOR USE

THE FOLLOWING COVERAGE POLICY APPLIES TO HEALTH BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. CERTAIN CIGNA COMPANIES AND/OR LINES OF BUSINESS ONLY PROVIDE UTILIZATION REVIEW SERVICES TO CLIENTS AND DO NOT MAKE COVERAGE DETERMINATIONS. REFERENCES TO STANDARD BENEFIT PLAN LANGUAGE AND COVERAGE DETERMINATIONS DO NOT APPLY TO THOSE CLIENTS. COVERAGE POLICIES ARE INTENDED TO PROVIDE GUIDANCE IN INTERPRETING CERTAIN STANDARD BENEFIT PLANS ADMINISTERED BY CIGNA COMPANIES. PLEASE NOTE, THE TERMS OF A CUSTOMER'S PARTICULAR BENEFIT PLAN DOCUMENT [GROUP SERVICE AGREEMENT, EVIDENCE OF COVERAGE, CERTIFICATE OF COVERAGE, SUMMARY PLAN DESCRIPTION (SPD) OR SIMILAR PLAN DOCUMENT] MAY DIFFER SIGNIFICANTLY FROM THE STANDARD BENEFIT PLANS UPON WHICH THESE COVERAGE POLICIES ARE BASED. FOR EXAMPLE, A CUSTOMER'S BENEFIT PLAN DOCUMENT MAY CONTAIN A SPECIFIC EXCLUSION RELATED TO A TOPIC ADDRESSED IN A COVERAGE POLICY. IN THE EVENT OF A CONFLICT, A CUSTOMER'S BENEFIT PLAN DOCUMENT ALWAYS SUPERSEDES THE INFORMATION IN THE COVERAGE POLICIES. IN THE ABSENCE OF A CONTROLLING FEDERAL OR STATE COVERAGE MANDATE, BENEFITS ARE ULTIMATELY DETERMINED BY THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT. COVERAGE DETERMINATIONS IN EACH SPECIFIC INSTANCE REQUIRE CONSIDERATION OF 1) THE TERMS OF THE APPLICABLE BENEFIT PLAN DOCUMENT IN EFFECT ON THE DATE OF SERVICE; 2) ANY APPLICABLE LAWS/REGULATIONS; 3) ANY RELEVANT COLLATERAL SOURCE MATERIALS INCLUDING COVERAGE POLICIES AND; 4) THE SPECIFIC FACTS OF THE PARTICULAR SITUATION. EACH COVERAGE REQUEST SHOULD BE REVIEWED ON ITS OWN MERITS. MEDICAL DIRECTORS ARE EXPECTED TO EXERCISE CLINICAL JUDGMENT WHERE APPROPRIATE AND HAVE DISCRETION IN MAKING INDIVIDUAL COVERAGE DETERMINATIONS. WHERE COVERAGE FOR CARE OR SERVICES DOES NOT DEPEND ON SPECIFIC CIRCUMSTANCES, REIMBURSEMENT WILL ONLY BE PROVIDED IF A REQUESTED SERVICE(S) IS SUBMITTED IN ACCORDANCE WITH THE RELEVANT CRITERIA OUTLINED IN THE APPLICABLE COVERAGE POLICY, INCLUDING COVERED DIAGNOSIS AND/OR PROCEDURE CODE(S). REIMBURSEMENT IS NOT ALLOWED FOR SERVICES WHEN BILLED FOR CONDITIONS OR DIAGNOSES THAT ARE NOT COVERED UNDER THIS COVERAGE POLICY (SEE "CODING INFORMATION" BELOW). WHEN BILLING, PROVIDERS MUST USE THE MOST APPROPRIATE CODES AS OF THE EFFECTIVE DATE OF THE SUBMISSION. CLAIMS SUBMITTED FOR SERVICES THAT ARE NOT ACCOMPANIED BY COVERED CODE(S) UNDER THE APPLICABLE COVERAGE POLICY WILL BE DENIED AS NOT COVERED. COVERAGE POLICIES RELATE EXCLUSIVELY TO THE ADMINISTRATION OF HEALTH BENEFIT PLANS. COVERAGE POLICIES ARE NOT RECOMMENDATIONS FOR TREATMENT AND SHOULD NEVER BE USED AS TREATMENT GUIDELINES. IN CERTAIN MARKETS, DELEGATED VENDOR GUIDELINES MAY BE USED TO SUPPORT MEDICAL NECESSITY AND OTHER COVERAGE DETERMINATIONS.

CIGNA NATIONAL FORMULARY COVERAGE:

OVERVIEW

Krazati, a Kirsten RAt Sarcoma (KRAS) inhibitor, is indicated for the following uses[1]:
- **Non-small cell lung cancer (NSCLC)**, treatment of *KRAS G12C*-mutated locally advanced or metastatic disease, as determined by an FDA-approved test, in adults who have received at least one prior systemic therapy.
- **Colorectal cancer**, in combination with Erbitux® (cetuximab intravenous infusion) for the treatment of *KRAS G12C*-mutated locally advanced or metastatic disease, as determined by an FDA-approved test, in adults who have received prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.

Both the NSCLC and colorectal cancer indications were approved under accelerated approval based on objective response rate and duration of response. Continued

approval for these indications may be contingent upon verification and description of a clinical benefit in confirmatory trials.

Mutations in the *KRAS* gene most commonly occur at codon 12.[2] Data suggest that approximately 30% of patients with NSCLC have *KRAS* mutations. The prognosis of survival of patients with tumors with *KRAS* mutation is poorer compared with that of patients with tumors without *KRAS* mutation.

Guidelines

National Comprehensive Cancer Network (NCCN) guidelines recommend Krazati in multiple conditions:

- **Ampullary Adenocarcinoma:** Guidelines (version 1.2025 – December 20, 2024) recommend Krazati for *KRAS G12C* mutation-positive disease for subsequent therapy for disease progression under "Useful in Certain Circumstances" for targeted systemic therapies (category 2A).[9]
- **Biliary Tract Cancer:** Guidelines (version 5.2024 – November 27, 2024) recommend Krazati for *KRAS G12C* mutation-positive tumors for subsequent-line therapy (category 2A).[6]
- **Central Nervous System (CNS) Cancers:** Guidelines (version 5.2024 – March 18, 2025) recommend Krazati for brain metastases due to *KRAS G12C* mutation-positive NSCLC (category 2A).[3] Lumakras™ (sotorasib tablets) is also recommended (category 2B). The guidelines have a general footnote that if an active agent exists (e.g., cytotoxic, targeted, immune modulating), trial of systemic therapy with good CNS penetration may be considered in select patients (e.g., small asymptomatic metastases) for initial treatment. This is also stated in the Compendium.[10] In addition, the agent can be considered as treatment for recurrent brain metastases and for treatment of relapsed disease with either stable systemic disease or reasonable systemic treatment options. This applies for both limited and extensive brain metastases.
- **Colon and Rectal Cancer:** Guidelines for colon cancer (version 4.2024 – July 3, 2024) and rectal cancer (version 3.2024 – July 3, 2024) recommend Krazati for some situations in patients with *KRAS G12C*-mutated disease.[4,5] For initial treatment in combination with Erbitux or Vectibix® (panitumumab intravenous infusion) or as monotherapy if patient is unable to tolerate Erbitux or Vectibix due to toxicity (category 2A). Krazati is also recommended as subsequent therapy (category 2A) after previous therapy with oxaliplatin, irinotecan, FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).
- **Non-Small Cell Lung Cancer:** Guidelines (version 1.2025 – December 20, 2024) recommend Krazati as a subsequent treatment option, for use after at least one prior systemic treatment (i.e., second-line and beyond) if the patient has not received previous *KRAS G12C*-targeted therapy (category 2A). Patients who progressed on Lumakras, another *KRAS* inhibitor directed at *KRAS G12C*-mutated NSCLC, should not be treated with Krazati; and vice-versa due to their similar mechanisms of action.
- **Pancreatic Adenocarcinoma:** Guidelines (version 1.2025 – December 20, 2024) recommend Krazati as "Useful in Certain Circumstances" for subsequent therapy (category 2A) for locally advanced/metastatic disease and therapy for

recurrent disease with *KRAS G12C* mutation-positive disease.[8] It is a category 2B recommendation for poor performance status.

- **Small Bowel Adenocarcinoma:** Guidelines (version 1.2025 – December 4, 2024) recommend Krazati as a second-line and subsequent therapy (if not previously given) for *KRAS G12C* mutation-positive disease (category 2A).[7]

POLICY STATEMENT

Prior Authorization is recommended for prescription benefit coverage of Krazati. All approvals are provided for the duration noted below.

- **Krazati™ (adagrasib tablets - Mirati Therapeutics)**

is(are) covered as medically necessary when the following criteria is(are) met for FDA-approved indication(s) or other uses with supportive evidence (if applicable):

FDA-Approved Indications

1. **Non-Small Cell Lung Cancer (NSCLC).** Approve for 1 year if the patient meets ALL of the following (A, B, and C):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has *KRAS G12C*-mutated locally advanced or metastatic NSCLC, as determined by an approved test; AND
   - **C)** Patient meets ONE of the following (i or ii):
     - **i.** Patient has been previously treated with at least one systemic regimen; OR
       Note: Examples of systemic regimens include those containing one or more of the following products: Keytruda (pembrolizumab intravenous infusion), Opdivo (nivolumab intravenous infusion), Tecentriq (atezolizumab intravenous infusion), Alimta (pemetrexed intravenous infusion), Yervoy (ipilimumab intravenous infusion), Abraxane (albumin-bound paclitaxel intravenous infusion), bevacizumab, cisplatin, carboplatin, docetaxel, gemcitabine, paclitaxel, vinorelbine.
     - **ii.** Patient has brain metastases.

2. **Colon or Rectal Cancer.** Approve for 1 year if the patient meets ALL of the following (A, B, C, D, and E):
   - **A)** Patient is ≥ 18 years of age; AND
   - **B)** Patient has unresectable, advanced, or metastatic disease; AND
   - **C)** Patient has *KRAS G12C* mutation-positive disease; AND
   - **D)** Patient meets ONE of the following (i or ii):
     - **i.** The medication is prescribed as part of a combination regimen for colon or rectal cancer; OR
       Note: Examples of combination regimens included Krazati + Erbitux (cetuximab intravenous infusion), Krazati + Vectibix (panitumumab intravenous infusion).
     - **ii.** As per the prescriber, the patient is unable to tolerate combination therapy; AND

E) Patient has previously received a chemotherapy regimen for colon or rectal cancer.
Note: Examples of chemotherapy regimens include a fluoropyrimidine such as 5-fluorouracil (5-FU), capecitabine; oxaliplatin, irinotecan, or an adjunctive chemotherapy regimen such as FOLFOX (5-FU, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

Other Uses with Supportive Evidence

3. Ampullary Adenocarcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has metastatic disease; AND
C) Patients has *KRAS G12C* mutation-positive disease; AND
D) The medication will be used as subsequent therapy.

4. Biliary Tract Cancer. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has unresectable and metastatic disease; AND
C) Patient has *KRAS G12C* mutation-positive disease; AND
D) Patient has been previously treated with at least one systemic regimen.
Note: Examples of systemic regimens include those containing one or more of the following products: Keytruda (pembrolizumab intravenous infusion), Imfinzi (durvalumab intravenous infusion), gemcitabine, cisplatin, carboplatin, capecitabine, oxaliplatin, FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin), 5-fluorouracil, Abraxane (albumin-bound paclitaxel intravenous infusion).

5. Pancreatic Adenocarcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, and C):
A) Patient is ≥ 18 years of age; AND
B) Patients has *KRAS G12C* mutation-positive disease; AND
C) Patient meets ONE of the following (i or ii):
i. Patient meets BOTH of the following (a and b):
a) Patient has locally advanced or metastatic disease; AND
b) Patient has been previously treated with at least one systemic regimen; OR
Note: Examples of systemic regimens include one or more of the following: gemcitabine, albumin-bound paclitaxel, capecitabine, Keytruda (pembrolizumab intravenous infusion), FOLFIRINOX (5-fluoruracil + leucovorin + irinotecan + oxaliplatin).
ii. Patient has recurrent disease after resection.

6. Small Bowel Adenocarcinoma. Approve for 1 year if the patient meets ALL of the following (A, B, C, and D):
A) Patient is ≥ 18 years of age; AND
B) Patient has advanced or metastatic disease; AND
C) Patient has *KRAS G12C* mutation-positive disease; AND

D) The medication will be used as subsequent therapy.

CONDITIONS NOT COVERED

- **Krazati™ (adagrasib tablets - Mirati Therapeutics)**

is(are) considered not medically necessary for ANY other use(s); criteria will be updated as new published data are available):

REFERENCES

1. Krazati™ tablets [prescribing information]. San Diego, CA: Mirati Therapeutics; June 2024.
2. The NCCN Non-Small Cell Lung Cancer Clinical Practice Guidelines in Oncology (version 1.2025 - December 20, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on January 5, 2025.
3. The NCCN Central Nervous System Cancers Clinical Practice Guidelines in Oncology (version 5.2024 – March 18, 2025). © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 9, 2025.
4. The NCCN Colon Cancer Clinical Practice Guidelines in Oncology (version 5.2024 – August 22, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on January 5, 2025.
5. The NCCN Rectal Cancer Clinical Practice Guidelines in Oncology (version 4.2024 – August 22, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on January 5, 2025.
6. The NCCN Biliary Tract Cancers Clinical Practice Guidelines in Oncology (version 5.2024 – November 27, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on January 5, 2025.
7. The NCCN Small Bowel Adenocarcinoma Clinical Practice Guidelines in Oncology (version 1.2025 – December 4, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on January 5, 2025.
8. The NCCN Pancreatic Adenocarcinoma Clinical Practice Guidelines in Oncology (version 1.2025 – December 20, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on January 5, 2025.
9. The NCCN Ampullary Adenocarcinoma Clinical Practice Guidelines in Oncology (version 1.2025 – December 20, 2024). © 2024 National Comprehensive Cancer Network. Available at: http://www.nccn.org/. Accessed on January 5, 2025.
10. The NCCN Drugs and Biologics Compendium. © 2025 National Comprehensive Cancer Network. Available at: http://www.nccn.org. Accessed on May 9, 2025. Search term: adagrasib.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	**Colon or Rectal Cancer:** Under "Other Uses with Supportive Evidence" added new condition of approval based on guideline recommendations.	12/20/2023
Update	DEU Update, 7/12/2024: Colon or Rectal Cancer is moved from Other Uses with Supportive Evidence to FDA-approved use for Krazati.	--
Annual Revision	**Ampullary Adenocarcinoma:** Under "Other Uses with Supportive Evidence" added new condition of approval and criteria. **Biliary Tract Cancer:** Under "Other Uses with Supportive Evidence" added new condition of approval and criteria. **Pancreatic Adenocarcinoma:** Under "Other Uses with Supportive Evidence" added new condition of approval and criteria.	01/08/2025

	Small Bowel Adenocarcinoma: Under "Other Uses with Supportive Evidence" added new condition of approval and criteria.	
Update	04/20/2025: The policy name was changed from "Oncology – Krazati PA Policy" to "Oncology (Oral – Kirsten RAt Sarcoma Virus Inhibitor) – Krazati PA Policy".	N/A
Selected Revision	**Non-Small Cell Lung Cancer (NSCLC):** Added criterion to allow use of Krazati for brain metastases.	05/14/2025

N/A – Not applicable.