Clinical Policy: Larotrectinib (Vitrakvi)

Reference Number: CP.PHAR.414
Effective Date: 01.15.18
Last Review Date: 02.26
Line of Business: Commercial, HIM, Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Larotrectinib (Vitrakvi®) is a first-generation selective tropomyosin receptor kinase (TRK) tyrosine kinase inhibitor (TKI).

FDA Approved Indication(s)

Vitrakvi is indicated for the treatment of adult and pediatric patients with solid tumors that:

- Have a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- Are metastatic or where surgical resection is likely to result in severe morbidity, and
- Have no satisfactory alternative treatments or that have progressed following treatment.

Select patients for therapy based on an FDA-approved test.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results, or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Vitrakvi is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. NTRK Fusion-Positive Cancer (must meet all)**:**

1. Diagnosis of one of the following (a or b):
   a. Solid tumor *(see Appendix D for examples)*;
   b. Histiocytic neoplasm (e.g., Erdheim-Chester disease, Langerhans Cell histiocytosis, Rosai-Dorfman disease) (*off-label*);
2. Prescribed by or in consultation with one of the following (a or b):
   a. Oncologist;
   b. For histiocytic neoplasm, a hematologist;
3. For Vitrakvi requests, member must use larotrectinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. Tumor is positive for an NTRK1/2/3-gene fusion (e.g., ETV6-NTRK3, TPM3-NTRK1);
5. Prescribed as a single agent;
6. Confirmation of no known acquired tropomyosin receptor kinase resistance mutation;
7. For solid tumor: Meets one of the following (a or b):
   a. Disease is persistent, recurrent, advanced, or metastatic;

b. Member has failed or is not a candidate for primary therapy (e.g., surgery, chemotherapy, radiation);

8. Request meets one of the following (a or b):
   a. Member must use Rozlytrek®^, unless contraindicated or clinically significant adverse effects are experienced;*
      ^Prior authorization may be required for Rozlytrek.
      **For Illinois HIM requests, the step therapy requirements above do not apply per IL HB 5395*
   b. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings *(see Appendix E)*;
9. For disease relapse or progression following Rozlytrek therapy, medical justification as to why additional NTRK targeted therapy is warranted;
10. Request does not exceed health-plan approved quantity limit;
11. Request meets one of the following (a, b, or c):*
    a. Adults and pediatric members with body surface area ≥ 1.0 m^2: Dose does not exceed one of the following (i or ii):
       i. 200 mg per day;
       ii. 400 mg per day and prescriber attestation of member's inability to avoid concomitant use of CYP3A4 inducer (e.g., St. John's wort);
    b. Pediatric members with body surface area < 1.0 m^2: Dose does not exceed one of the following (i or ii):
       i. 200 mg/m^2 per day;
       ii. 400 mg/m^2 per day and prescriber attestation of member's inability to avoid concomitant use of CYP3A4 inducer (e.g., St. John's wort);
    c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

    **Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. NTRK-Fusion Positive Cancer (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Vitrakvi for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Prescribed as a single agent;
4. For Vitrakvi requests, member must use larotrectinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. Request does not exceed health-plan approved quantity limit;
6. If request is for a dose increase, request meets one of the following (a, b, or c):*
   a. Adults and pediatric members with body surface area ≥ 1.0 m^2: New dose does not exceed one of the following (i or ii):
      i. 200 mg per day;
      ii. 400 mg per day and prescriber attestation of member's inability to avoid concomitant use of CYP3A4 inducer (e.g., St. John's wort);
   b. Pediatric members with body surface area < 1.0 m2: New dose does not exceed one of the following (i or ii):
      i. 200 mg/m^2 per day;
      ii. 400 mg/m^2 per day and prescriber attestation of member's inability to avoid concomitant use of CYP3A4 inducer (e.g., St. John's wort);
   c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN.*

Approval duration:
Medicaid/HIM – 12 months
Commercial – 12 months or duration of request, whichever is less

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid, or evidence of coverage documents;

B. Known acquired tropomyosin receptor kinase resistance mutation.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network
NTRK: neurotrophic receptor tyrosine kinase
TKI: tyrosine kinase inhibitor
TRK: tropomyosin receptor kinase

Appendix B: Therapeutic Alternatives

<table>
<tr><th>Drug Name</th><th>Dosing Regimen</th><th>Dose Limit/ Maximum Dose</th></tr>
<tr><td>Rozlytrek®
(entrectinib)</td><td><u>NTRK fusion-positive cancer</u>
Adults: 600 mg PO QD
Pediatrics by body surface area (BSA):
<table>
<tr><th>Age</th><th>Recommended daily dosage</th></tr>
<tr><td>> 6 months</td><td>≤ 0.50 m^2: 300 mg/m^2 PO QD
0.51 to 0.80 m^2: 200 mg PO QD
0.81 to 1.10 m^2: 300 mg PO QD
1.11 to 1.50 m^2: 400 mg PO QD
≥1.51 m^2: 600 mg PO QD</td></tr>
<tr><td>> 1 month to ≤ 6 months</td><td>250 mg/m^2 PO QD</td></tr>
</table></td><td>Adults: 600 mg/day

Pediatrics: see regimen</td></tr>
</table>

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: Examples of Solid Tumors

(Examples are drawn from the Vitrakvi pivotal trials, as described in the FDA prescribing information, as well as the National Comprehensive Center Network (NCCN) Vitrakvi compendium.)

- Ampullary adenocarcinoma
- Appendiceal neoplasm and cancers (e.g., appendiceal adenocarcinoma, goblet cell adenocarcinoma, undifferentiated carcinoma not otherwise specified)
- Biliary tract cancers (e.g., extrahepatic/intrahepatic cholangiocarcinoma, gallbladder cancer)
- Breast cancer

- Central nervous system cancers (e.g., circumscribed glioma/glioneural tumors, pleomorphic xanthoastrocytoma, glioblastoma, gliosarcoma, H3-mutated high-grade glioma, high-grade astrocytoma with piloid features, brain metastases)
- Cholangiocarcinoma
- Colorectal cancer
- Esophageal and esophagogastric junction cancer
- Gastric cancer
- Gastrointestinal stromal tumors
- Gynecological cancers (e.g., epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer, uterine cancers, vaginal cancer, vulvar cancer, cervical cancer)
- Head and neck cancers (e.g., salivary gland tumors)
- Hepatocellular carcinoma
- Melanoma
- Neuroendocrine and adrenal tumors (extrapulmonary poorly differentiated)
- Non-small cell lung cancer
- Occult primary
- Pancreatic adenocarcinoma
- Pediatric central nervous system cancers (e.g., diffuse high-grade glioma)
- Small bowel adenocarcinoma
- Soft tissue sarcoma (e.g., epithelioid hemangioendothelioma, extremity/body wall, head/neck, retroperitoneal/intraabdominal, solitary fibrous tumor, infantile fibrosarcoma, gastrointestinal stromal tumor)
- Thyroid carcinoma (e.g., anaplastic, follicular, oncocytic, papillary)

Appendix E: States with Regulations against Redirections in Cancer

State	Step Therapy Prohibited?	Notes
FL	Yes	For stage 4 metastatic cancer and associated conditions.
GA	Yes	For stage 4 metastatic cancer. Redirection does not refer to review of medical necessity or clinical appropriateness.
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA.
IN	Yes	For advanced, metastatic cancer and associated conditions
LA	Yes≠	For stage 4 advanced, metastatic cancer or associated conditions. ≠Exception if clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy.
MS	Yes	For advanced metastatic cancer and associated conditions
NV	Yes	Stage 3 and stage 4 cancer patients for a prescription drug to treat the cancer or any symptom thereof of the covered person
OH	Yes	For stage 4 metastatic cancer and associated conditions
OK	Yes	For advanced metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes^	For cancer and associated conditions

State	Step Therapy Prohibited?	Notes
		^Exception if step therapy is for AB-rated generic equivalent, interchangeable biological product, or biosimilar product to the equivalent brand drug
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
NTRK fusion-positive solid tumors	• Adult and pediatric patients with body surface area ≥ 1.0 m^2: 100 mg PO BID until disease progression or until unacceptable toxicity • Pediatric patients with body surface area < 1.0 m^2: 100 mg/m^2 PO BID until disease progression or until unacceptable toxicity	200 mg/day

VI. Product Availability

- Capsules: 25 mg, 100 mg
- Oral solution (100 mL bottle): 20 mg/mL

VII. References

1. Vitrakvi Prescribing Information. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; April 2025. Available at: www.vitrakvi-us.com. Accessed November 6, 2025.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed November 6, 2025.
3. Drilon A, Laetsch TW, Kummar S, et al. Efficay of larotrectinib in TRK fusion-positive cancers in adults and children. N Eng J Med 2018;378:731-9. DOI:10,1056/NEJMoa1714448.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2022 annual review: added histiocytic neoplasm indication per NCCN category 2A with allowance for hematology specialty; clarified NTRK fusion-positive cancer could also be persistent per NCCN; added Legacy WellCare auth durations (WCG.CP.PHAR.414 to be retired); allowed by-passing of redirection if state regulations do not allow step therapy in Stage IV or metastatic cancer settings and added Appendix E; references reviewed and updated.	12.06.21	02.22
Revised approval duration for Commercial line of business from length of benefit to 12 months or duration of request, whichever is less	01.20.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	09.23.22	

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q 2023 annual review: no significant changes; Legacy WellCare approval durations consolidated to 6/12 months; references reviewed and updated.	11.14.22	02.23
Updated Appendix E to include Oklahoma.	06.07.23	
1Q 2024 annual review: in Appendix B, updated Rozlytrek recommended doses per updated PI; in Appendix D, added central nervous system cancers to example solid tumors; references reviewed and updated.	11.20.23	02.24
Added Mississippi to Appendix E.	06.05.24	
1Q 2025 annual review: for Appendix D, added ampullary adenocarcinoma, biliary tract cancers, esophageal and esophagogastric junction cancer, head and neck cancers, uterine neoplasms, vaginal cancer, and vulvar cancer to example of solid tumors as supported by NCCN compendium; references reviewed and updated.	11.01.24	02.25
RT4: updated indication from accelerated approval to traditional full approval. Updated Appendix E with revised language and exception for Tennessee.	06.17.25	
1Q 2026 annual review: added required use as a single agent; added approval pathway for members who failed or are not candidates for primary therapy (e.g., surgery, chemotherapy, or radiation); added step therapy bypass for IL HIM per IL HB 5395; added requirement that request does not exceed health-plan approved quantity limit; added dose maximum and prescriber attestation for concomitant use with CYP3A4 inducers; extended Medicaid and HIM initial approval duration from 6 months to 12 months for this maintenance medication for a chronic condition; references reviewed and updated.	11.06.25	02.26
Updated Appendix E to include Indiana.	03.26.26	
Updated Appendix E with revised language for Tennessee.	06.24.26	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health

plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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