Clinical Policy: Entrectinib (Rozlytrek)

Reference Number: CP.PHAR.441
Effective Date: 12.01.19
Last Review Date: 11.25
Line of Business: Commercial, HIM, Medicaid

Revision Log

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

Description

Entrectinib (Rozlytrek®) is a kinase inhibitor.

FDA Approved Indication(s)

Rozlytrek is indicated for the treatment of:

- Adult patients with ROS1-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.
- Adult and pediatric patients older than 1 month of age with solid tumors that:*
  - have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion as detected by an FDA-approved test without a known acquired resistance mutation,
  - are metastatic or where surgical resection is likely to result in severe morbidity, and
  - have either progressed following treatment or have no satisfactory alternative therapy.

**This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.*

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 Rozlytrek is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Non-Small Cell Lung Cancer (must meet all)**:**

1. Diagnosis of recurrent, advanced, or metastatic NSCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is ROS1 positive;*
   **See criteria set I.B for NTRK fusion-positive NSCLC*
5. Prescribed as single agent;
6. For brand Rozlytrek requests, member must use generic entrectinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed any of the following (i, ii, and iii):
      i. 600 mg per day;
      ii. 3 capsules per day;
      iii. 12 packets per day;

b. 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. 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 neoplasms (e.g., Langerhans cell, Erdheim-Chester disease, 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. Age > 1 month;
4. For solid tumor: Meets one of the following (a or b):
   a. Disease is advanced, metastatic, recurrent, or unresectable;
   b. Member has failed or is not a candidate for primary therapy (e.g., surgery, chemotherapy, radiation);
5. Tumor is positive for an NTRK gene fusion (e.g., ETV6-NTRK3, TPM3-NTRK1) without a known resistance mutation;
6. Prescribed as a single agent;
7. For brand Rozlytrek requests, member must use generic entrectinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
8. Member has not received prior NTRK targeted therapy (e.g., Vitrakvi®, Augtyro®);
9. Documentation of member's current body surface area (BSA) (m^2);
10. Request meets one of the following (a, b, c, or d):*
    a. Adults: Dose does not exceed any of the following (i, ii, and iii):
       i. 600 mg per day;
       ii. 3 capsules per day;
       iii. 12 packets per day;
    b. Pediatrics age > 6 months: Dose does not exceed any of the following (i – v):
       i. BSA ≥ 1.51 m^2 (1, 2, and 3):
          1) 600 mg PO QD;
          2) 3 capsules per day;
          3) 12 packets per day;
       ii. BSA 1.11 to 1.50 m^2 (1, 2, and 3):
          1) 400 mg PO QD;
          2) 2 capsules per day;
          3) 8 packets per day;
       iii. BSA 0.81 to 1.10 m^2: (1, 2, and 3):
          1) 300 mg PO QD;
          2) 2 capsules per day;
          3) 6 packets per day;

iv. BSA 0.51 to 0.80 m^2: (1, 2, and 3):
1) 200 mg PO QD;
2) 1 capsule per day;
3) 4 packets per day;

v. BSA ≤ 0.50 m^2: (1, 2, and 3):
1) 300 mg/m^2 PO QD;
2) 1 capsule per day;
3) 3 packets per day;

c. Pediatrics age > 1 month to ≤ 6 months: Dose does not exceed 250 mg/m^2 per day;
d. 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

C. Melanoma (off-label) (must meet all):
1. Diagnosis of cutaneous melanoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Disease is ROS1 positive;*
   **See criteria set I.B for NTRK fusion-positive melanoma*
5. Prescribed as a single agent, as second-line or subsequent therapy;
6. For brand Rozlytrek requests, member must use generic entrectinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
7. Request meets one of the following (a or b):*
   a. Dose does not exceed both of the following (i, ii, and iii):
      i. 600 mg per day;
      ii. 3 capsules per day;
      iii. 12 packets per day;
   b. 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

D. 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. All Indications in Section I (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Rozlytrek for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If member has a diagnosis of NTRK fusion-positive cancer, documentation of member's current BSA (m^2);
4. For brand Rozlytrek requests, member must use generic entrectinib, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. If request is for a dose increase, request meets one of the following (a, b, c, or d):*
   a. Adults: New dose does not exceed any of the following (i, ii, and iii):
      i. 600 mg per day;
      ii. 3 capsules per day;
      iii. 12 packets per day;
   b. Pediatrics age > 6 months: New dose does not exceed any of the following (i – v):
      i. BSA ≥ 1.51 m^2 (1, 2, and 3):
         1) 600 mg PO QD;
         2) 3 capsules per day;
         3) 12 packets per day;
      ii. BSA 1.11 to 1.50 m^2 (1, 2, and 3):
         1) 400 mg PO QD;
         2) 2 capsules per day;
         3) 8 packets per day;
      iii. BSA 0.81 to 1.10 m^2 (1, 2, and 3):
         1) 300 mg PO QD;
         2) 2 capsules per day;
         3) 6 packets per day;
      iv. BSA 0.51 to 0.80 m^2: (1, 2, and 3):
         1) 200 mg PO QD;
         2) 1 capsule per day;
         3) 4 packets per day;
      v. BSA ≤ 0.50 m^2: (1, 2, and 3):
         1) 300 mg/m^2 PO QD;
         2) 1 capsule per day;
         3) 3 packets per day;

c. Pediatrics age > 1 month to ≤ 6 months: New dose does not exceed 250 mg/m^2 per day;
d. 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.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

BSA: body surface area
FDA: Food and Drug Administration
NCCN: National Comprehensive Cancer Network
NSCLC: non-small cell lung cancer
NTRK: neurotrophic tyrosine receptor kinase

Appendix B: Therapeutic Alternatives
Not applicable

Appendix C: Contraindications/Boxed Warnings
None reported

Appendix D: Examples of Solid Tumors
(Examples are drawn from the Rozyltrek pivotal trials, as described in the FDA prescribing information, as well as the National Comprehensive Center Network (NCCN) Rozyltrek compendium.)

- Ampullary adenocarcinoma
- Biliary tract cancers (e.g., extrahepatic and intrahepatic cholangiocarcinoma, gallbladder cancer)
- Breast cancer
- Carcinoma not otherwise specified (adenocarcinoma or squamous cell carcinoma)
- Central nervous system cancers (e.g., circumscribed glioma, glioblastoma, brain metastases)
- Colon cancer (including appendiceal adenocarcinoma)
- Cutaneous melanoma
- Esophageal and esophagogastric junction cancers
- Gastric cancers
- Gastrointestinal stromal tumors
- Gynecological cancers (e.g., epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer, uterine cancers, vaginal cancers, vulvar cancers, cervical cancers)
- Hepatocellular carcinoma
- Lung cancer
- Neuroendocrine cancers
- Pancreatic cancer
- Rectal cancer
- Salivary gland tumor
- Small bowel adenocarcinoma
- Soft tissue sarcoma (e.g., epithelioid hemangioendothelioma, retroperitoneal/intraabdominal, angiosarcoma, rhabdosarcoma/rhabdomyosarcoma, sarcoma of the extremity, solitary fibrous tumor, superficial trunk, undifferentiated pleomorphic sarcoma, extremity/body wall, or head/neck)
- Thyroid cancer (papillary, oncocytic/Hurthle cell, anaplastic, or follicular carcinoma)

V. Dosage and Administration

<table>
<tr><th>Indication</th><th>Dosing Regimen</th><th>Maximum Dose</th></tr>
<tr><td>ROS1-positive NSCLC</td><td>Adults: 600 mg PO QD</td><td>600 mg/day</td></tr>
<tr><td>NTRK fusion-positive solid tumor</td><td>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>
</table></td><td>Adults: 600 mg/day

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

Indication	Dosing Regimen		Maximum Dose
	Age	Recommended daily dosage	
	> 1 month to ≤ 6 months	250 mg/m^2 PO QD	

VI. Product Availability

- Capsules: 100 mg, 200 mg
- Pellet: 50 mg

VII. References

1. Rozlytrek Prescribing Information. South San Francisco, CA: Genentech USA, Inc.; January 2024. Available at: www.rozlytrek.com. Accessed July 23, 2025.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed July 25, 2025.
3. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 7.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed July 25, 2025.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
4Q 2021 annual review: no significant changes; added redirection to generic product once available; revised HIM.PHAR.21 to HIM.PA.154; added legacy WCG auth duration (WCG.CP.PHAR.441 to retire); references reviewed and updated.	06.23.21	11.21
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
4Q 2022 annual review and RT4: updated FDA approved indication section to include "FDA-approved companion diagnostic" to mirror prescribing information; WCG-specific policy was retired and that 12 month approval duration was consolidated to 6 months; references reviewed and updated. Template changes applied to other diagnoses/indications and continued therapy section.	08.09.22	11.22
4Q 2023 annual review: no significant changes; references reviewed and updated.	08.10.23	11.23
RT4: for NTRK solid tumors, updated age limit to > 1 month from ≥ 12 years per newly FDA-approved pediatric extension; updated recommended dosages per PI; added new oral pellet formulation; for NSCLC, removed exclusion for members who previously received ROS1 therapy per NCCN and FDA; references reviewed and updated	11.20.23	
4Q 2024 annual review: for NSCLC, added requirement for use as a single agent; for NTRK solid tumors, added requirement for recurrent or unresectable disease and use as a single agent per	08.07.24	11.24

Reviews, Revisions, and Approvals	Date	P&T Approval Date
NCCN; added off-label criteria for ROS1 positive melanoma per NCCN 2A recommendation; in continued therapy, added requirement that member must use generic if available; clarified solid tumors examples Appendix D per NCCN compendium; references reviewed and updated.		
4Q 2025 annual review: revised NTRK fusion-positive solid tumor section to NTRK fusion-positive cancer to include off-label non-solid tumor indications; for NTRK fusion-positive cancer, added criteria for histiocytic neoplasms per NCCN 2A recommendation with allowance for hematology specialty, added option for advanced disease for solid tumors, and revised maximum capsules for pediatrics per PI; for all indications, extended initial approval duration for Medicaid and HIM from 6 months to 12 months for this maintenance medication for a chronic condition; references reviewed and updated.	07.25.25	11.25

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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

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.