Clinical Policy: Entrectinib (Rozlytrek)
Reference Number: CP.PHAR.441
Effective Date: 12.01.19
Last Review Date: 11.19
Line of Business: Commercial, TBD HIM*, Medicaid

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

*For Health Insurance Marketplace members, if request is through the pharmacy benefit, this policy applies only when the referenced drug is on the health plan approved formulary. Request for non-formulary drugs must be reviewed using the policy: HIM.PA.103.

Description
Entrectinib (Rozlytrek™) is a kinase inhibitor.

FDA Approved Indication(s)
Rozlytrek is indicated for the treatment of:
- Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive.
- Adult and pediatric patients 12 years of age and older with solid tumors that:
  - have a neurotrophic tyrosine receptor 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 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;
5. Member has not received prior ROS1 targeted therapy (e.g., Xalkori®, Zykadia®, Lorbrena®);
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 600 mg (3 capsules) 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 – 6 months
Commercial – Length of Benefit

B. NTRK Fusion-Positive Solid Tumor (must meet all):
1. Diagnosis of a solid tumor (see Appendix D for examples);
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Meets one of the following (a or b):
   a. Disease is metastatic;
   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. Member has not received prior NTRK targeted therapy (e.g., Vitrakvi®);
7. Request meets one of the following (a, b, or c):*
   a. Adults: Dose does not exceed 600 mg (3 capsules) per day;
   b. Pediatrics: Dose does not exceed any of the following (i, ii, or iii):
      i. BSA > 1.50 m²: 600 mg PO QD;
      ii. BSA 1.11 to 1.50 m²: 500 mg PO QD;
      iii. BSA 0.91 to 1.10 m²: 400 mg PO QD;
   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 – 6 months
Commercial – Length of Benefit

C. Other diagnoses/indications
1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.CPA.09 for commercial, HIM.PHAR.21 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 request is for a dose increase, request meets one of the following (a, b, or c):*
   a. Adults: New dose does not exceed 600 mg (3 capsules) per day;
   b. Pediatrics: New dose does not exceed any of the following (i, ii, or iii):
      i. BSA > 1.50 m²: 600 mg PO QD;
ii. BSA 1.11 to 1.50 m²: 500 mg PO QD;
iii. BSA 0.91 to 1.10 m²: 400 mg PO QD;

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 – Length of Benefit

**B. Other diagnoses/indications** (must meet 1 or 2):
1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   - **Approval duration:** Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized); CP.CPA.09 for commercial, HIM.PHAR.21 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.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

**IV. Appendices/General Information**

**Appendix A: Abbreviation/Acronym Key**
- 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.)
- Breast cancer
- Cholangiocarcinoma
- Colorectal cancer
- Gynecological cancers (e.g., epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer)
- Lung cancer
• Neuroendocrine cancers  
• Pancreatic cancer  
• Salivary gland tumor  
• Soft tissue sarcoma (e.g., retroperitoneal/intraabdominal, angiosarcoma, rhabdosarcoma, sarcoma of the extremity, superficial trunk, or head/neck)  
• Thyroid cancer (papillary, Hurthle cell, anaplastic, or follicular carcinoma)

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROS1-positive NSCLC Adults:</td>
<td>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 (≥ 12 years of age) by body surface area (BSA):</td>
<td>600 mg/day</td>
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<tr>
<td></td>
<td>• BSA &gt; 1.50 m²: 600 mg PO QD</td>
<td></td>
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<tr>
<td></td>
<td>• BSA 1.11 to 1.50 m²: 500 mg PO QD</td>
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<td></td>
<td>• BSA 0.91 to 1.10 m²: 400 mg PO QD</td>
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VI. Product Availability
Capsules: 100 mg, 200 mg

VII. References

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
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<tbody>
<tr>
<td>Policy created.</td>
<td>10.01.19</td>
<td></td>
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<tr>
<td>Ad hoc change: NTRK fusion tumors: no known resistance mutation added for clarity, pediatric dosing details added.</td>
<td>11.19.19</td>
<td></td>
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**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.

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