Clinical Policy Title:	entrectinib
Policy Number:	RxA.270
Drug(s) Applied:	Rozlytrek™
Original Policy Date:	02/07/2020
Last Review Date:	06/10/2021
Line of Business Policy Applies to:	All lines of business

Background

Entrectinib (Rozlytrek™) is a kinase inhibitor. It 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 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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
entrectinib (Rozlytrek™)	*ROS1*-positive NSCLC	Adults: 600 mg by mouth once daily	600 mg/day
	NTRK fusion-positive solid tumor	Adults: 600 mg by mouth once daily Pediatrics (age ≥ 12) by body surface area (BSA): • BSA > 1.50 m^2: 600 mg by mouth once daily • BSA 1.11 to 1.50 m^2: 500 mg by mouth once daily . BSA 0.91 to 1.10 m^2: 400 mg by mouth once daily	600 mg/day

Dosage Forms

- Capsules: 100 mg, 200mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the term of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

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. Prescribed as monotherapy;
4. 18 years of age or older;
5. Disease is *ROS1* positive;
6. Member has not received prior ROS1 targeted therapy (e.g., Xalkori®, Zykadia®, Lorbrena®);
7. 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:
Commercial: 6 months
Medicaid: 6 months

B. NTRK Fusion-Positive Solid Tumor (must meet all):

1. Diagnosis of a solid tumor (see Appendix D for examples and NCCN 2A recommended uses);
2. Prescribed by or in consultation with an oncologist;
3. Prescribed as monotherapy;
4. 12 years of age or older;
5. 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);
6. Tumor is positive for an NTRK gene fusion (e.g., ETV6-NTRK3, TPM3-NTRK1) without a known resistance mutation;
7. Member has not received prior NTRK targeted therapy (e.g., Vitrakvi®);
8. 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 m^2: 600 mg by mouth once daily;
      ii. BSA 1.11 to 1.50 m^2: 500 mg by mouth once daily;
      iii. BSA 0.91 to 1.10 m^2: 400 mg by mouth once daily;
   c. Dose is within FDA maximum limit for any FDA approved indication or 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
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

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

1. Member is currently receiving medication that has been authorized by RxAdvance or member has met initial approval criteria for the covered indications 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 m^2: 600 mg by mouth once daily;
      ii. BSA 1.11 to 1.50 m^2: 500 mg by mouth once daily;
      iii. BSA 0.91 to 1.10 m^2: 400 mg by mouth once daily;
   c. New dose is within FDA maximum limit for any FDA approved indication or 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
Commercial: 12 months
Medicaid: 12 months

III. Appendices

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
BSA: Body surface area

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug	Dosing Regimen	Dose Limit/Maximum Dose
Vitrakvi® (larotectinib)	**For Solid Tumors with the NTRK mutation:** • Adult and pediatric patients with body surface area ≥ 1.0 m^2 : 100 mg by mouth twice daily until disease progression or until unacceptable toxicity • Pediatric patients with body surface area < 1.0 m^2 : 100 mg/m2 by mouth twice daily until disease progression or until unacceptable toxicity	200 mg/day
Xalkori® (crizotinib)	**For NSCLC with ROS1 mutation:** 250 mg by mouth twice daily	500 mg/day

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

- Contraindication(s):
  - None Reported

- Boxed Warning(s):
  - None Reported

APPENDIX D: General Information

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
- Gynaecological 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)

NCCN 1 and 2A level Recommendation for use of Rozlytrek:

- Esophageal and Esophagogastric Junction Cancer - Palliative therapy for patients with NTRK gene fusion-positive tumor
- Invasive Breast Cancer - Single agent therapy for recurrent unresectable (local or regional) or stage IV (M1) disease with NTRK gene-fusion tumor
- Central Nervous System Cancers (Limited or Extensive Brain Metastases) - Single-agent treatment with NTRK gene-fusion tumor
- Colon Cancer - Single agent therapy for progression of metastatic disease (NTRK gene fusion positive)
- Gastric Cancer - Palliative therapy for patients with NTRK gene fusion-positive tumor
- Gastrointestinal Stromal Tumors (GIST) - Single agent for NTRK gene-fusion positive tumor (useful in certain circumstances)
- Head and Neck Cancers - Salivary Gland Tumors: Useful in certain circumstances as systemic therapy for NTRK gene fusion-positive recurrent disease
- Hepatobiliary Cancers (Hepatocellular Carcinoma) - single agent for progressive disease in patients (NTRK gene fusion positive)
- Hepatobiliary Cancers (Gallbladder Cancer) - useful in certain circumstances
- Histiocytic Neoplasms (Langerhans Cell Histiocytosis, Erdheim-Chester Disease, Rosai-Dorfman Disease) - First-line or subsequent therapy for neurotrophic tyrosine kinase (NTRK) gene fusion target as a single agent, useful in certain circumstances,
- Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer - Single-agent therapy (useful in certain circumstances) for disease persistence or recurrence in NTRK gene-fusion positive tumors
- Pancreatic Adenocarcinoma - Useful in certain circumstances only for patients with NTRK gene fusion-positive tumors
- Rectal Cancer - Subsequent therapy as a single agent for progression of metastatic disease (NTRK gene fusion positive)

- Small Bowel Adenocarcinoma - Subsequent therapy for metastatic disease that is NTRK gene fusion positive
- Soft Tissue Sarcoma - Useful in certain circumstances as first-line advanced/metastatic therapy for NTRK gene fusion positive sarcomas
- Thyroid Carcinoma - For NTRK gene fusion positive tumors

References

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Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
Policy was reviewed: 1. Policy title table was updated. 2. Initial approval criteria updated: - I.A.3 and I.B.3 added to specify prescribing method. - I.B.6 updated to be more specific. - I.B.8 added for dosing requirements. 3. Continued Therapy Approval criteria was updated to add II.A.3 for dosing requirements. 4. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 5. Approval duration in initial approval and Continued Therapy was updated. 6. QD was updated with once daily in document. 7. References were updated	08/27/2020	09/14/2020
Policy was reviewed: 1. PO, BID was updated with by mouth & Twice daily in document. 2. Appendix A: Abbreviation/Acronym Key Added for BSA 3. Appendix B: Therapeutic Alternatives added 4. Updated Appendix D to include NCCN 1 and 2A recommended uses 5. References were added and updated.	03/24/2021	06/10/2021