entrectinib (Rozlytrek®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO082

Description

Entrectinib (Rozlytrek) is an orally administered selective kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
entrectinib (Rozlyrek)	Neurotrophic receptor tyrosine kinase gene fusion positive solid tumors Non-small cell lung cancer, metastatic, ROS1-positive	50 mg pellets	**Pediatric:** Dosing per body surface area* to the nearest full-size package
		100 mg capsules	30 capsules/30 days
		200 mg capsules	90 capsules/30 days

**See appendix for body surface area dosing for pediatric patients with NTRK positive solid tumors*

Initial Evaluation

I. **Entrectinib (Rozlytrek)** may be considered medically necessary when the following criteria below are met:
   A. Prescribed by or in consultation with an oncologist; **AND**
   B. Medication will not be used in combination with any other oncolytic medication; **AND**
   C. A diagnosis of one of the following:
      1. **Solid tumor with a confirmed NTRK gene fusion**; **AND**
         i. Member is one month of age or older; **AND**
         ii. If member is under the age of 18, the member's body surface area (BSA) is submitted; **AND**
         iii. Member has metastatic disease; **OR**
            a. Surgical resection is likely to result in severe morbidity (i.e., tumor is unresectable); **AND**
         iv. Member does not have an acquired resistance mutation; **AND**
         v. Attestation that all alternative therapies for diagnosis and stage of cancer have been exhausted as defined by:
            a. Progression following all appropriate treatments; **OR**
            b. Nonresponse to all available therapies; **OR**
            c. All available therapies are contraindicated or not tolerated; **OR**

d. No standard or satisfactory treatments exist; **OR**

2. **ROS1-positive non-small cell lung cancer as detected by an FDA-approved test**; **AND**
   i. Member is 18 years of age or older; **AND**
   ii. Member has not progressed on any previous ROS1 targeted therapy [e.g., crizotinib (Xalkori), ceritinib (Zykadia), lorlatinib (Lorbrena), etc.]

II. Entrectinib (Rozlytrek) is considered investigational when used for all other conditions, including but not limited to:
   A. Non-small cell lung cancer without NTRK fusion or ROS1-positive gene rearrangements (e.g., ALK-positive NSCLC)
   B. Solid tumors that do not harbor NTRK gene fusions

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Medication will not be used in combination with any other oncolytic medication; **AND**
IV. Response to therapy as indicated by stabilization of disease or decrease in tumor size or spread.

Supporting Evidence

I. Entrectinib (Rozlytrek) is currently FDA approved for adult patients with a *ROS1*-positive metastatic non-small cell lung cancer (NSCLC) and received an accelerated approval in 2019 for adult and pediatric patients ages 12 and older for neurotrophic tyrosine receptor kinase (NTRK) positive solid tumors, metastatic or where surgical resection is likely to cause severe morbidity. In October 2023, this accelerated approval in NTRK solid tumors was expanded to include age one month and older.
II. Due to the complexity of treatment and diagnosis, of either indication, it is recommended that patients are seen by, or in consultation with an oncologist.
III. Neither therapy is approved to be used in combination with another oncolytic medication; therefore, entrectinib (Rozlytrek) should be used as monotherapy.
IV. Safety and efficacy data for entrectinib (Rozlytrek) is available through the following clinical trials: Phase 2 STARTRK-2, Phase 1 STARTRK-2, Phase 1 ALKA-372-001, and Phase 1/2 STARTRK-NG and TAPISTRY. The last two supporting approval in pediatric subjects.

- STARTRK2: Basket study of entrectinib (Rozlytrek) for the treatment of patients with solid tumors harboring NTRK1/2/3, ROS1 or ALK gene rearrangements (fusions). This pivotal trial was non-randomized, open-label and analyzed 206 subjects for safety. For efficacy, data was captured for 51 NTRK fusion-positive and 37 ROS1-positive subjects.
- STARTRK1: A Phase I, single-arm, open-label study evaluated the same population parameters as STARTRK2, and included 76 subjects for the safety evaluation. Two subjects with NTRK fusion-positive and 7 subjects with ROS1-positive disease were evaluated for efficacy.
- ALKA-372-001: A Phase I, single-arm, open-label study evaluated the same population in STARTRK1 and 2. Safety data was gathered from 57 subjects. One subject had NTRK fusion-positive and 9 subjects had ROS1-positive disease were evaluated for efficacy.
- STARTRK-NG: A Phase I/IIb, single-arm, open-label study evaluated dose escalation and expansion in children and adolescents with recurrent or refractory solid tumors with or without TRK, ROS1, or ALK fusions. No subjects were included that had NTRK fusion-positive or ROS1-positive NSCLC. Twenty-nine subjects were evaluated. In 2023, this was expanded to include NTRK and ROS1 gene fusions; 15 subjects with NTRK 1/2/3 and eight with ROS1 were included in the primary outcomes.
- TAPISTRY: Phase 2, open-label, multi-cohort study in patients with locally advanced, unresectable, or metastatic solid tumors. This trial tests multiple different treatment arms and mutation types. For entrectinib (Rozlytrek), recruitment of 50 subjects for ROS1 arm and 200 patients for the NTRK arm is being projected. The trial does not conclude until 2032.

NTRK Positive Solid Tumors

V. Data for NTRK fusion-positive solid tumor FDA-approval for adult patients included a pooled group of 54 subjects across the trials listed above. Patients were mainly white, female with a median age of 58, and 96% of patients had metastatic disease, including 22% with CNS metastases, and 4% had locally advanced, unresectable disease. All patients had received prior treatment for their cancer including surgery (n = 43), radiotherapy (n = 36), or systemic therapy (n = 48). Forty patients (74%) received prior systemic therapy for metastatic disease with one prior systemic regimen and 17% (n = 9) received 3 or more prior systemic regimens. The primary outcome was an objective response rate (ORR) of: 59% (43-71), with 46% achieving partial response (PR) and 13% achieving complete response (CR).

VI. Data for NTRK fusion positive solid tumor in pediatric patients included 33 patients from the last two trials listed above. Patients were on average four years of age, white with locally advanced disease (71%) or metastatic disease (29%) with 85% of patients having prior therapy for their cancer including surgery (n=20), radiotherapy (n=7) and/or systemic therapy (n=22). The

primary endpoint was ORR which was 70% (51-84) with 27% having a partial response (PR) and 42% having a complete response (CR).

ROS1-positive NSCLC

VII. Data for ROS1-positive NSCLC FDA-approved included a pooled 92 subjects across the trials listed above with the primary outcome of ORR: 74% (64-83), 59% with PR and 15% CR.

VIII. NTRK fusions are found in a wide variety of cancers and are generally mutually exclusive from other targetable oncogenic drivers. There is a lack of standard of care and these patients are generally treated according to the histological tumor type and do not have targeted therapy. There is only one other agent, larotrectinib (Vitrakvi), for a similar setting to entrectinib (Rozlytrek). It was FDA-approved less than one year before entrectinib (Rozlytrek) in November 2018. The medication was evaluated in those that had progressed following treatment or had no satisfactory treatment alternative(s). Additionally, subjects that had metastatic disease or surgical resection were likely to result in severe morbidity.

IX. ROS1-positive NSCLC is a rare subtype of NSCLC, accounting for only 1-2% of all cases. ROS1-positive NSCLC is a progressive disease with the most common site of metastases being the CNS. Currently, the NCCN 1.2024 NSCLC guidelines recommend entrectinib, crizotinib, repotrectinib or ceritinib as preferred therapy for ROS1- positive NSCLC. Crizotinib (Xalkori) is FDA-approved, but has limited data for safety and efficacy and has not been shown to target CNS metastases. Ceritinib (Zykadia) has been used in some instances, which may have more CNS activity; however, safety and efficacy data is very limited and it is not FDA-approved for ROS1-positive NSCLC. Repotrectinib (Augtyro) did allow those with CNS activity in the study as long as stable, responses were shown in seven of the eight patients. Entrectinib (Rozlytrek) has shown some CNS activity, and in clinical trials five of seven subjects with CNS metastases showed CNS response.

X. In clinical trials dose interruption occurred in 46% of subjects, and dose reduction was required in 28%. Grade 3-4 adverse drug events occurred in 60% of subjects in the trial.

XI. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Investigational or Not Medically Necessary Uses

I. Entrectinib (Rozlytrek) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:

A. Non-small cell lung cancer without NTRK fusion or ROS1-positive gene rearrangements (e.g., ALK-positive NSCLC)
    i. Due to the mechanism of action, investigation in ALK-positive NSCLC is underway; however, safety and efficacy have not been defined.
B. Solid tumors that do not harbor NTRK gene fusions
    i. Efficacy and safety of entrectinib (Rozlytrek) in solid tumors without NTRK fusions has not been sufficiently evaluated.

Appendix

I. Table 1: Pediatric dosing for NTRK gene fusion positive solid tumors

Body Surface Area (BSA)	Recommended Dosage, Orally, once daily
≤0.5 m^2	300 mg/m^2
0.51 to 0.80 m^2	200 mg
0.81 to 1.10 m^2	300 mg
1.11 to 1.50 m^2	400 mg
≥1.51 m^2	600 mg

- In general, the average BSA for a newborn child is 0.25m^2; a two- year-old is 0.5m^2; a five-year-old child is 0.77m^2; a ten-year-old child is 1.14m^2.

References

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2. Farago AF, Le LP, Zheng Z, et al. Durable Clinical Response to Entrectinib in NTRK1-Rearranged Non-Small Cell Lung Cancer. J Thorac Oncol. 2015;10(12):1670-4.
3. Sigal D, Tartar M, Xavier M, et al. Activity of Entrectinib in a Patient With the First Reported Fusion in Neuroendocrine Cancer. J Natl Compr Canc Netw. 2017;15(11):1317-1322.
4. Gatalica Z, Xiu J, Swensen J, Vranic S. Molecular characterization of cancers with NTRK gene fusions. Mod Pathol. 2019;32(1):147-153.
5. Vitrakvi [Prescribing Information]. Loxo Oncology, Inc. Stamford, CT. 2023
6. Xalkori [Prescribing Information]. Pfizer Labs. 2023.
7. Augtyro [Prescribing Information]. Bristol Myers Squibb. Princeton, NJ. 2023.
8. Demetri, G.D., et al., Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: Pooled analysis of STARTRK-2, STARTRK-1, and ALKA-372- 001. Ann Oncol, 2018. 29(S9).
9. National comprehensive Cancer Network. NCCN Guidelines. Soft Tissue Sarcoma: Version 3.2023. Available at: sarcoma.pdf (nccn.org)
10. Desai AV, Robinson GW, Gauvain K, et al. Entrectinib in children and young adults with solid or primary CNS tumors harboring NTRK, ROS1, or ALK aberrations (STARTRK-NG). *Neuro Oncol*. 2022;24(10):1776-1789.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
larotrectinib (VITRAKVI®)	NTRK Gene Fusion Positive Solid Tumors
ALK+ Inhibitors	Non-Small Cell Lung Cancer

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated initial approval duration from three months to six months. Updated new age expansion for NTRK positive solid tumors in patients one month and older. Removal of specialist requirement upon renewal, removal of toxicity assessment upon renewal, and addition of standard sample renewal language. Updated supporting evidence across all indications. Updated references and added related policy table.	02/2024
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Previous Reviews	09/2019 11/2019