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: Three months, split fill
- Renewal: Six months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
entrectinib (Rozlyrek)	100 mg capsules	Neurotrophic receptor tyrosine kinase gene fusion positive solid tumors	30 capsules/30 days	207677
	200 mg capsules	Non-small cell lung cancer, metastatic, ROS1-positive	90 capsules/30 days	207687

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 12 years of age or older; **AND**
         ii. Member has metastatic disease, **OR** surgical resection is likely to result in severe morbidity (i.e., tumor is unresectable); **AND**
         iii. Member does not have an acquired resistance mutation; **AND**
         iv. 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. Prescribed by or in consultation with an oncologist; **AND**
II. Medication will not be used in combination with any other oncolytic medication; **AND**
III. Response to therapy as indicated by stabilization of disease or decrease in tumor size or spread; **AND**
IV. Member does not have unacceptable medication toxicity (e.g., heart failure, hepatotoxicity, hyperuricemia, QT interval prolongation, vision disturbances, fracture, etc.).

Supporting Evidence

I. 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 which included 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.

II. Data for NTRK fusion-positive solid tumor FDA-approval included a pooled group of 54 subjects across the trials listed above. The primary outcome was an objective response rate (ORR) of: 57% (43-71), with 50% achieving partial response (PR) and 7.4% achieving complete response (CR).

III. Data for ROS1-positive NSCLC FDA-approved included a pooled 51 subjects across the trials listed above with the primary outcome of ORR: 78% (65-89), 73% with PR and 6% CR.

IV. 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). 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.

V. 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. Crizotinib (Xalkori) is FDA-approved, but has limited data for safety and efficacy and has not been shown to target CNS mets. 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. Entrectinib (Rozlytrek) has shown some CNS activity, and in clinical trials five of seven subjects with CNS metastases showed CNS response.

VI. 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.

VII. In all trials, entrectinib (Rozlytrek) was evaluated for safety and efficacy as monotherapy.

VIII. Specific resistance mutations have not been identified via label for entrectinib (Rozlytrek) as they have been for lorotrectinib (Vitrakvi).

Investigational or Not Medically Necessary Uses

I. Due to the mechanism of action, investigation in ALK-positive NSCLC is underway; however, safety and efficacy have not been defined.

II. Efficacy and safety of entrectinib (Rozlytrek) in solid tumors without NTRK fusions has not been sufficiently evaluated.

References

1. Rozlytrek [Prescribing Information]. Genentech. San Francisco, CA. 2019.
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. 2018
6. Xalkori [Prescribing Information]. Pfizer Labs. 2017.
7. 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).
8. Clinicaltrials.gov

Policy Implementation/Update:

Date Created	September 2019
Date Effective	November 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date