larotrectinib (Vitrakvi®)

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO042

Description

Larotrectinib (Vitrakvi) is an orally administered tropomyosin receptor kinase (TRK) inhibitor; specifically TRKA, TRKB, and TRKC.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
larotrectinib (Vitrakvi)	25 mg capsule	Neuotrophic receptor tyrosine kinase gene fusion positive solid tumor, metastatic	180 tablets/30 days
	100 mg capsule		60 tablets/30 days
	20 mg/1 mL solution		Quantity calculated to 100 mg/m2 of body surface area

Initial Evaluation

I. Larotrectinib (Vitrakvi) may be considered medically necessary when the following criteria 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. The member has **not** previously progressed on other NTRK gene fusion medications (e.g., entrectinib [Rozlytrek]); **AND**
   D. A diagnosis of solid tumor with confirmed **NTRK gene fusion (e.g., gastrointestinal, thyroid, salivary gland); AND**
   E. NTRK gene fusion is determined using PT-PCR, FISH, or NGS testing methods; **AND**
   F. Member has metastatic disease, or surgical resection is likely to result in severe morbidity (i.e., tumor is unresectable); **AND**
   G. The member does **not** have an acquired resistance mutation (resistant mutations include, but may not be limited to, G595R, G623R, G696A, F617L); **AND**
   H. All alternative therapies for diagnosis and stage of cancer have been exhausted, as defined by:
      1. Progression following all appropriate treatments; **OR**
      2. Nonresponse to all available therapies; **OR**

3. All available therapies are contraindicated or not tolerated; **OR**
4. No standard or satisfactory treatments exist; **AND**

I. The member has intolerance to, or contraindication to, entrectinib (Rozlytrek); **OR**
   1. Member is less than 12 years of age

II. Larotrectinib (Vitrakvi) is considered not medically necessary when criteria above are not met and/or when used for the following:
   A. When used for a resistance mutation (resistant mutations include, but may not be limited to G595R, G623R, G696A, F617L)

III. Larotrectinib (Vitrakvi) is considered investigational when used for all other conditions, including but not limited to:
   A. Oncolytic indications as an adjunct therapy
   B. Non-small cell lung cancer without NTRK fusion gene rearrangements
   C. Solid tumors that do not harbor NTRK gene fusions
   D. Leukemias or lymphomas

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Prescribed by, or in consultation with, an oncologist; **AND**
IV. Medication will **not** be used in combination with any other oncolytic medication; **AND**
V. Response to therapy as indicated by stabilization of disease or decrease in tumor size or spread; **AND**
VI. Member does **not** have unacceptable medication toxicity (e.g., hepatotoxicity, severe delirium or gait disturbances, etc.); **AND**
VII. Documentation of absence of acquired resistance

Supporting Evidence

I. Per the landmark trials LOXO-TRK-14001 (SCOUT and NAVIGATE): All subjects were diagnosed with measurable or evaluable metastatic or locally advanced solid tumors, had progressed beyond all effective and available therapies per the National Comprehensive Cancer Network

(NCCN), had no therapies available for the diagnosis per NCCN guidelines, or surgical resection would result in significant morbidity.

II. Subjects were without acquired resistance mutations to NTRK-inhibitors, without active cardiovascular disease or history of myocardial infarction within the prior six months and were not on concurrent YP3A4 inhibitors or inducers.

III. The NTRK gene fusion mutation was confirmed using a validated laboratory testing method. Testing methods for NTRK gene fusion include NGS, RT-PCR, FISH, or Immunohistochemistry (ICH). The use of ICH may lead to a false positive result. ICH uses the presence of a surrogate marker (TRK proteins) to establish the likelihood of a NTRK gene fusion. The FISH method requires the visual assessment of an experienced pathologist of several tests and is considered more subjective than NGS or RT-PCR.

IV. The trials were single-arm, open-label studies that included 55 patients with solid tumors. The tumor types that had represented AND reported a measurable Overall Response Rate (ORR) were the following:

- Salivary gland cancer
- Soft tissue sarcoma (STS)
- Infantile fibrosarcoma (IFS)
- Gastrointestinal Stromal Tumor (GIST)
- Non-small cell lung cancer (NSCLC)
- Colorectal cancer (CRC)
- Melanoma
- Thyroid carcinoma
- Colon cancer

V. Those tumors that were evaluated in one or more subjects but did not show an ORR includ cholangiocarcinoma, appendix, breast and pancreatic cancer.

VI. Adverse reactions were common with larotrectinib (Vitrakvi), and included fatigue, pyrexia, peripheral edema, CNS, gastrointestinal, respiratory, musculoskeletal, and laboratory disturbances (e.g., ASK, ALT). Adverse events leading to dose discontinuation, interruption or reduction occurred in 37% of subjects. The safety profile of larotrectinib (Vitrakvi) is likely not fully developed given the small number of subjects in the clinical trials and short trial duration. Additionally, due to rarity of the NTRK gene fusion mutation, post-marketing information is likely to remain limited.

VII. There are currently two available therapies for NTRK gene fusion positive mutations. Larotrectinib (Vitrakvi) and entrectinib (Rozlytrek), currently there is no direct comparison data showing safety and/or efficacy differences between these therapies OR safety or efficacy of using them sequentially after progression. Additionally, caution should be exercised when making cross trial comparisons. At this time, entrectinib (Rozlytrek) provides a better value for

general populations with NTRK gene fusion positive tumors given the sum of safety, efficacy, and cost information currently available.

VIII. It should also be noted that due to single-arm, open-label trial designs, as well as outcomes evaluated, no NTRK gene fusion therapies available have been shown to improve health outcomes to date.

IX. Entrectinib (Rozlytrek) is FDA-approved down to 12 years of age, but has and will continue to be evaluated in younger populations. Larotrectinib (Vitrakvi) FDA-approval is nonspecific to pediatrics and adults.

Investigational or Not Medically Necessary Uses

I. Larotrectinib (Vitrakvi) does not have sufficient activity in those with resistance mutations. As of December 2019, known resistance mutations include: G595R, G623R, G696A, F617L.

II. Larotrectinib (Vitrakvi) has not been sufficiently evaluated for safety and efficacy in the following settings:
   A. Oncolytic indications as an adjunct therapy
   B. Non-small cell lung cancer without NTRK fusion gene rearrangements
   C. Solid tumors that do not harbor NTRK gene fusions
   D. Leukemias or lymphomas

References

1. Vitrakvi [Prescribing Information]. Stamford, CT: Loxo Oncology,Inc. November 2018.
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3. Gatalica Z, Swensen J, Kimbrough J, et. al. AACR-NCI-EORTC 2017. Abstract A047: Molecular characterization of the malignancies with targetable NTRK gene fusions. Available at: http://mct.aacrjournals.org/content/17/1_Supplement/A047. Accessed December 5, 2018.
4. Hyman DM, Laetsch TW, Kummar S, et al. ASCO 2017. Abstract LBA2501: The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.18_suppl.LBA2501. Accessed December 5, 2018.
5. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med*. 2018 Feb 22;378(8):731-739. doi: 10.1056/NEJMoa1714448.
6. Heymach J, Krilov L, Alberg A, et al. Clinical Cancer Advances 2018: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology. *J Clin Oncol,* Vol 36, No 10 (April 1), 2018: pp 1020-1044. DOI: https://doi.org/10.1200/JCO.2017.77.0446

Policy Implementation/Update:

Date Created	January 2019
Date Effective	February 2019
Last Updated	December 2019
Last Reviewed	December 2019

Action and Summary of Changes	Date
Policy updated to newest formatting. Initial approval duration changed to three months from six months given safety concerns and split-fill designation, quantity limit for solution now based on BSA, removal of designated test requirement, removed requirements for lab value monitoring, requirement for lack of CV comorbidities and CNS symptoms. Addition of monotherapy requirement, documentation of intolerance of contraindication to entrectinib (Rozlytrek) and requirement the member has not previously progressed on other NTRK therapies.	12/2019