RXADVANCE
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Clinical Policy Title:	larotrectinib
Policy Number:	RxA.555
Drug(s) Applied:	Vitrakvi®
Original Policy Date:	03/06/2020
Last Review Date:	12/07/2020
Line of Business Policy Applies to:	All lines of business

Background

Larotrectinib (Vitrakvi®) is a first-generation selective tropomyosin receptor kinase (TRK) tyrosine kinase inhibitor (TKI). It is indicated for the treatment of adult and pediatric patients with solid tumors that:

- Have a neurotrophic receptor tyrosine 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 no satisfactory alternative treatments or that have progressed following treatment

Limitation of use(s):
This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
larotrectinib (Vitrakvi®)	NTRK fusion-positive solid tumors	• Adult and pediatric patients with body surface area ≥ 1.0 m^2: 100 mg PO BID until disease progression or until unacceptable toxicity • Pediatric patients with body surface area < 1.0 m^2: 100 mg/m^2 PO BID until disease progression or until unacceptable toxicity	200 mg/day

Dosage Forms

- Capsules: 25 mg, 100 mg
- Oral solution (100 mL bottle): 20 mg/mL

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.

I. Initial Approval Criteria

A. NTRK Fusion-Positive Cancer (must meet all):

1. Diagnosis of a solid tumor with both characteristics (a and b):
   a. Tumor is positive for NTRK-gene fusion;
   b. Disease is metastatic or surgical resection is likely to result in severe morbidity;
2. Disease has progressed following initial treatment or medical justification supports that there are no appropriate alternative treatments;
3. Documentation of no known acquired tropomyosin receptor kinase resistance mutation;
4. Prescribed by or in consultation with an oncologist;
5. Member has not received prior NTRK targeted therapy (e.g., Rozlytrek®);
6. Request meets one of the following (a or b):
   a. Dose does not exceed 200 mg/day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval Duration
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. NTRK-Fusion Positive Cancer (must meet all):

1. Member is Currently receiving medication that has been authorized by RxAdvance, or documentation supports that member is currently receiving Vitrakvi® 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 or b):
   a. New dose does not exceed 200 mg/day;
   b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
NCCN: National Comprehensive Center Network
NTRK: neurotrophic receptor tyrosine kinase
TKI: tyrosine kinase inhibitor
TRK: tropomyosin receptor kinase
FISH: Fluorescent in situ hybridization
NGS: Next generation sequencing
IHC: Immunohistochemistry assay

APPENDIX B: Therapeutic Alternatives

Vitrakvi® should be used following progression after initial therapy that is standard of care for the specific solid tumor type based on NCCN guidelines, unless there are no such alternative therapies available.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported
- Boxed Warning(s):
  - None reported

APPENDIX D: General Information

- There exists a higher incidence (60 to 100%) of NTRK-fusion mutation in certain rare solid tumor types (e.g., secretory breast cancer, secretory salivary gland, infantile fibrosarcoma, mesoblastic nephroma), while there exists a much lower (about 1%) incidence of NTRK-fusion mutations in more common tumor types (e.g., colorectal cancer, lung cancer, melanoma).
- Currently, there are no FDA-approved tests available yet for the detection of NTRK gene fusion, but Loxo Oncology is partnering with Ventana Medical Systems to develop a panTRK fusion IHC test as a companion diagnostic for Vitrakvi®.
- Acceptable laboratory diagnostic tests for NTRK-mutation status include:
  - Fluorescent in situ hybridization (FISH) or Next generation sequencing (NGS)
  - Immunohistochemistry assay (IHC)
- Examples of Solid Tumors (Examples are drawn from the Vitrakvi® pivotal trials, as described in the FDA prescribing information, as well as the National Comprehensive Center Network (NCCN) Vitrakvi® compendium.)
  - Cancer of the appendix
  - Breast cancer
  - Cholangiocarcinoma
  - Colorectal cancer
  - Gynecological cancers (e.g., epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer)
  - Lung cancer
  - Melanoma
  - Neuroendocrine cancers
  - Pancreatic cancer
  - Salivary gland tumor
  - Small bowel adenocarcinoma
  - Soft tissue sarcoma (e.g., retroperitoneal/intraabdominal, angiosarcoma, rhabdosarcoma, sarcoma of the extremity, superficial trunk, or head/neck, infantile fibrosarcoma, gastrointestinal stromal tumor)

References

1. Vitrakvi® Prescribing Information. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; July 2019. Available at: www.vitrakvi.com. Accessed October 08, 2020.
2. Drilon A, Laetsch TW, Kummar S, et al. Efficay of larotrectinib in TRK fusion-positive cancers in adults and children. N Eng J Med 2018; 378:731-739. Accessed October 08, 2020.
3. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed October 08, 2020.
4. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2020. Accessed with subscription at: http://www.clinicalkey.com. Updated January 14, 2020. Accessed October 08, 2020.

5. Larotrectinib, Lexi-Drug. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed with subscription at: http://online.lexi.com. Accessed October 08, 2020.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Policy title table was updated: Line of business policy applies was updated to All lines of business. 2. Initial approval criteria I.A.5 was added "Member has not received prior NTRK targeted therapy." 3. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". 4. Approval duration was updated HIM removed, Commercial approval duration has been updated from length of benefit to 6 months and 12 months for initial and continued therapy approval, respectively. 5. Appendix A: FISH, IHC and NGS were added. 6. Appendix D: Examples of solid cancers were added. 7. References were updated.	10/08/2020	12/07/2020