09-J3000-25

Original Effective Date: 04/01/19

Reviewed: 02/13/19

Revised: 01/15/20

Subject: Larotrectinib (Vitrakvi)

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Neurotrophic receptor tyrosine kinase genes, NTRK1, NTRK2 and NTRK3, encode tropomysin receptor kinase (TRK) proteins (TRK-A,-B,-C). Chromosomal rearrangements involving these genes with various partners can result in TRK fusions that promote cell proliferation and survival in tumor cell lines. Larotrectinib (Vitrakvi®) is a kinase inhibitor of all three TRK proteins that has demonstrated anti-tumor activity in cells. It had minimal activity in clinically identified acquired resistance mutations in the TRKA kinase domain (G595R) and in the TRKC kinase domain (G623R, G696A, and F617L). Larotrectinib (Vitrakvi®) was Food and Drug Administration (FDA) approved in November 2018 for the treatment of adult and pediatric patients with solid tumors that have a 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 have progressed following treatment.

Larotrectinib was evaluated in pediatric and adult patients with unresectable or metastatic solid tumors with a NTRK gene fusion in three open-label, single-arm trials. Adults received 100 mg orally twice daily and pediatric patients received 100 mg/m^2 up to the maximum adult dose until disease progression or unacceptable toxicity. Patients were included if they had progressed following systemic therapy if available or would have required surgery with significant morbidity for locally advanced disease. Metastatic disease was present in 82% of patients and 18% had locally advanced, unresectable disease. The majority of patients (98%) had received prior treatment including surgery, radiotherapy, or systemic therapy. NTRK gene fusion status was evaluated using next generation sequencing (NGS) or fluorescence in situ hybridization (FISH). A total of 50 patients had NTRK gene fusions detected by NGS and 5 were detected by FISH. Overall response rate (ORR) and duration of response (DOR) were the primary efficacy outcomes and assessed by a blinded independent review committee. The ORR was 75% with 22% achieving a complete response and 53% a partial response. The ORR by tumor type with 4 or more patients included the following: soft tissue sarcoma (11 patients, 91%), salivary gland (12, patients, 83%), infantile fibrosarcoma (7 patients, 100%), thyroid (5 patients, 100%), lung (4 patients, 75%), melanoma (4 patients, 50%), colon (4 patients, 25%). ORR was assessed in patients with NTRK

Fusion partner ETV6-NTRK3 (25 patients,84%) and TPM3-NTRK1 (9 patients, 56%). The median duration of response has not yet been reached (range, 1.6+ - 33.2+ months) and 73% of patient had a DOR of greater than or equal to 6 months. The most common adverse events occurring at 20% or greater included fatigue, nausea, dizziness, vomiting, increased AST, cough, increased ALT, constipation, and diarrhea.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of larotrectinib (Vitrakvi®) **meets the definition of medical necessity** for members diagnosed with **ANY** of the following conditions in Table 1 when **ALL** of the indication specific criteria are met:

Table 1

CNS cancer - Brain metastases	When **ALL** of the following are met: 1. Member has brain metastases 2. Member's solid tumor is classified as NTRK gene fusion positive using FISH, RT-PCR, or NGS testing – documentation must be provided 3. Member does not have any known larotrectinib resistance mutations (e.g., G595R, G667S, F589L, A608D in the TRKA kinase domain or G623R, G696A, or F617L in the TRKC kinase domain) 4. Larotrectinib will be used as monotherapy 5. Dose does not exceed the following*: a. Adults and pediatrics with BSA of at least 1 meter-squared: 100 mg twice daily b. Pediatrics with BSA less than 1 meter-squared: 100 mg/m2 twice daily
Colon or rectal cancer	When **ALL** of the following are met: 1. Member has unresectable or metastatic disease 2. Member's solid tumor is classified as NTRK gene fusion positive using FISH, RT-PCR, or NGS testing – documentation must be provided 3. Member does not have any known larotrectinib resistance mutations (e.g., G595R, G667S, F589L, A608D in the TRKA kinase domain or G623R, G696A, or F617L in the TRKC kinase domain) 4. Larotrectinib is used as subsequent therapy after disease progression on initial treatment 5. Larotrectinib will be used as monotherapy 6. Dose does not exceed the following*: a. Adults and pediatrics with BSA of at least 1 meter-

	squared: 100 mg twice daily b. Pediatrics with BSA less than 1 meter-squared: 100 mg/m^2 twice daily
Melanoma	When **ALL** of the following are met: 1. Member has unresectable or metastatic disease 2. Member's solid tumor is classified as NTRK gene fusion positive using FISH, RT-PCR, or NGS testing – documentation must be provided 3. Member does not have any known larotrectinib resistance mutations (e.g., G595R, G667S, F589L, A608D in the TRKA kinase domain or G623R, G696A, or F617L in the TRKC kinase domain) 4. Larotrectinib is used as second-line or subsequent therapy after disease progression on initial treatment 5. Larotrectinib will be used as monotherapy 6. Dose does not exceed the following*: a. Adults and pediatrics with BSA of at least 1 meter-squared: 100 mg twice daily b. Pediatrics with BSA less than 1 meter-squared: 100 mg/m^2 twice daily
Non-Small Cell Lung Cancer	When **ALL** of the following are met: 1. Member has **ONE** of the following: a. Unresectable or metastatic disease b. Mediastinal lymph node recurrence and member has received prior radiation therapy 2. Member's solid tumor is classified as NTRK gene fusion positive using fluorescence in situ hybridization (FISH), reverse transcription polymerase chain reaction (RT-PCR), or next generation sequencing (NGS) testing – documentation must be provided 3. Member does not have any known larotrectinib resistance mutations (e.g., G595R, G667S, F589L, A608D in the TRKA kinase domain or G623R, G696A, or F617L in the TRKC kinase domain) 4. **ONE** of the following: a. Larotrectinib is used as first line therapy b. Larotrectinib is used as subsequent therapy after disease progression on initial non-NTRK-targeted treatment 5. Larotrectinib will be used as monotherapy 6. Dose does not exceed the following*: a. Adults and pediatrics with BSA of at least 1 meter-squared: 100 mg twice daily b. Pediatrics with BSA less than 1 meter-squared: 100 mg/m^2 twice daily
NTRK gene fusion positive solid	When **ALL** of the following are met:

tumors (not otherwise specified)	1. Member has unresectable or metastatic disease 2. Member's solid tumor is classified as NTRK gene fusion positive using FISH, RT-PCR, or NGS testing – documentation must be provided 3. Member does not have any known larotrectinib resistance mutations (e.g., G595R, G667S, F589L, A608D in the TRKA kinase domain or G623R, G696A, or F617L in the TRKC kinase domain) 4. **ONE** of the following: a. Larotrectinib is used as subsequent therapy after disease progression on initial treatment b. Member has no alternative treatment options 5. Larotrectinib will be used as monotherapy 6. Dose does not exceed the following*: a. Adults and pediatrics with BSA of at least 1 meter-squared: 100 mg twice daily b. Pediatrics with BSA less than 1 meter-squared: 100 mg/m^2 twice daily
Ovarian cancer (includes epithelial ovarian, fallopian tube, primary peritoneal cancer)	When **ALL** of the following are met: 1. Member has recurrent disease 2. Member's solid tumor is classified as NTRK gene fusion positive using FISH, RT-PCR, or NGS testing – documentation must be provided 3. Member does not have any known larotrectinib resistance mutations (e.g., G595R, G667S, F589L, A608D in the TRKA kinase domain or G623R, G696A, or F617L in the TRKC kinase domain) 4. Larotrectinib is used as subsequent therapy after disease progression on initial treatment 5. Larotrectinib will be used as monotherapy 6. Dose does not exceed the following*: a. Adults and pediatrics with BSA of at least 1 meter-squared: 100 mg twice daily b. Pediatrics with BSA less than 1 meter-squared: 100 mg/m2 twice daily
Pancreatic cancer	When **ALL** of the following are met: 1. Member has locally advanced, unresectable, recurrent, or metastatic disease 2. Member's solid tumor is classified as NTRK gene fusion positive using FISH, RT-PCR, or NGS testing – documentation must be provided 3. Member does not have any known larotrectinib resistance mutations (e.g., G595R, G667S, F589L, A608D in the TRKA kinase domain or G623R, G696A, or F617L in the TRKC kinase domain) 4. Larotrectinib will be used as monotherapy 5. Dose does not exceed the following*:

	a. Adults and pediatrics with BSA of at least 1 meter-squared: 100 mg twice daily b. Pediatrics with BSA less than 1 meter-squared: 100 mg/m^2 twice daily
Salivary gland tumors	When **ALL** of the following are met: 1. Member has recurrent disease with distant metastases 2. Member's solid tumor is classified as NTRK gene fusion positive using FISH, RT-PCR, or NGS testing – documentation must be provided 3. Member does not have any known larotrectinib resistance mutations (e.g., G595R, G667S, F589L, A608D in the TRKA kinase domain or G623R, G696A, or F617L in the TRKC kinase domain) 4. Larotrectinib will be used as monotherapy 5. Dose does not exceed the following*: a. Adults and pediatrics with BSA of at least 1 meter-squared: 100 mg twice daily b. Pediatrics with BSA less than 1 meter-squared: 100 mg/m^2 twice daily
Small bowel adenocarcinoma	When **ALL** of the following are met: 1. Member has unresectable or metastatic disease 2. Member's solid tumor is classified as NTRK gene fusion positive using FISH, RT-PCR, or NGS testing – documentation must be provided 3. Member does not have any known larotrectinib resistance mutations (e.g., G595R, G667S, F589L, A608D in the TRKA kinase domain or G623R, G696A, or F617L in the TRKC kinase domain) 4. Larotrectinib is used as subsequent therapy after disease progression on initial treatment 5. Larotrectinib will be used as monotherapy 6. Dose does not exceed the following*: a. Adults and pediatrics with BSA of at least 1 meter-squared: 100 mg twice daily b. Pediatrics with BSA less than 1 meter-squared: 100 mg/m2 twice daily
Soft Tissue Sarcoma	When **ALL** of the following are met: 1. When used for **ONE** of the following: a. Angiosarcoma b. Pleomorphic rhabdomyosarcoma c. Sarcoma of the extremity/superficial trunk/head/neck d. Unresectable, recurrent, progressive, or metastatic retroperitoneal/intraabdominal sarcoma 2. Member's solid tumor is classified as NTRK gene fusion positive using FISH, RT-PCR, or NGS testing – documentation must be provided

	3. Member does not have any known larotrectinib resistance mutations (e.g., G595R, G667S, F589L, A608D in the TRKA kinase domain or G623R, G696A, or F617L in the TRKC kinase domain) 4. Larotrectinib will be used as monotherapy 5. Dose does not exceed the following*: a. Adults and pediatrics with BSA of at least 1 meter-squared: 100 mg twice daily b. Pediatrics with BSA less than 1 meter-squared: 100 mg/m^2 twice daily
Thyroid cancer	When **ALL** of the following are met: 1. When used for **ONE** of the following: a. Anaplastic thyroid cancer b. Follicular, Hurthle Cell, or Papillary carcinoma when **ALL** of the following are met: i. Member disease is resistant to radioiodine treatment ii. Member has **ONE** of the following: 1. Unresectable locoregional disease that is recurrent or persistent 2. Distant metastatic disease 2. Member's solid tumor is classified as NTRK gene fusion positive using FISH, RT-PCR, or NGS testing – documentation must be provided 3. Member does not have any known larotrectinib resistance mutations (e.g., G595R, G667S, F589L, A608D in the TRKA kinase domain or G623R, G696A, or F617L in the TRKC kinase domain) 4. Larotrectinib will be used as monotherapy 5. Dose does not exceed the following*: a. Adults and pediatrics with BSA of at least 1 meter-squared: 100 mg twice daily b. Pediatrics with BSA less than 1 meter-squared: 100 mg/m^2 twice daily
Other FDA-approved or NCCN supported diagnosis (not previously listed above)	When **ALL** of the following are met: 1. ONE of the following is met: a. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert) b. Indication AND usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation

	2. Dose does not exceed the maximum FDA-approved dosing*

Approval duration: 90 days

Continuation of larotrectinib (Vitrakvi) **meets the definition of medical necessity** for the indications in Table 1 when **ALL** of the following criteria are met:

1. An authorization or reauthorization for larotrectinib has been previously approved by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met **ALL** indication-specific criteria for coverage.
2. Member's disease has not progressed during treatment with larotrectinib
3. Larotrectinib will be used as monotherapy
4. The dose does not exceed the following*:
    a. Adults and pediatrics with BSA of at least 1 meter-squared: 100 mg twice daily
    b. Pediatrics with BSA less than 1 meter-squared: 100 mg/m^2 twice daily

Approval duration: 6 months

*If capsules requested, using the fewest number of capsules per day

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

- 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.
- Select patients based on the presence of a NTRK gene fusion
- BSA 1 meter-squared: 100 mg orally twice daily
- BSA less than 1 meter-squared: 100 mg/m^2 orally twice daily

Dose Adjustments

- Reduce the starting dose by 50% in patients with moderate to severe hepatic impairment
- Withold for Grade 3 or 4 adverse reactions until resolution of improvement to baseline or grade 1. Resume at the next dosage modification if resolution occurs within 4 weeks. See prescribing information for dose modifications for adverse reactions. Permanently discontinue if an adverse reaction does not resolve within 4 weeks.
- Avoid coadministration of strong CYP3A4 inhibitors and strong CYP3A4 inducers. See prescribing information for dose adjustments if coadminstration cannot be avoided.

Drug Availability

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

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

- Neurotoxicity: patients and caretakers should be advised of the risk of neurologic adverse reactions and should not drive or operate hazardous machinery if neurotoxicity occurs. Withhold, modify, or permanently discontinue based on severity.
- Hepatotoxicity: Monitor liver tests including ALT and AST every 2 weeks during the first month of treatment, then monthly thereafter and as clinically indicated. Withhold, modify, or permanently discontinue based on severity.
- Embryo-fetal toxicity: Can cause fetal harm. Female patient should be advised of potential risk to fetus and to use effective contraception.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

C9399	Unclassified drugs or biologicals
J8999	Prescription drug, oral, chemotherapeutic, not otherwise specified

ICD-10 Diagnosis Codes That Support Medical Necessity

C07	Malignant neoplasm of parotid gland
C08.0 – C08.9	Malignant neoplasm of other and unspecified salivary glands
C17.0 – 17.2	Malignant neoplasm of duodenum, jejunum, ileum
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0 – C21.8	Malignant neoplasm of colon, rectosigmoid junction, rectum and anus and anal canal
C25.0 – C25.9	Malignant neoplasm of pancreas
C33	Malignant neoplasm of trachea

C34.00 – C34.02	Malignant neoplasm of unspecified main bronchus
C34.10 – C34.12	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.2	Malignant neoplasm of middle lobe, unspecified bronchus or lung
C34.30 – C34.32	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.80 – C34.82	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.90 – C34.92	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C43.0 – C43.9	Malignant melanoma of skin
C47.0 – C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48.0 – C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0 – C49.9	Malignant neoplasm of other connective and soft tissue
C56.1 – C56.9	Malignant neoplasm of ovary
C57.00-C57.9	Malignant neoplasm of other and unspecified female genital organs
C73	Malignant neoplasm of thyroid gland
C78.00 – C78.02	Secondary malignant neoplasm of unspecified lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31	Secondary malignant neoplasm of brain

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: BCBSF has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

DEFINITIONS:

None

RELATED GUIDELINES:

09-J3000-48, Entrectinib (Rozlytrek) Capsules

OTHER:

None

REFERENCES:

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the BCBSF Pharmacy Policy Committee on 02/13/19.

GUIDELINE UPDATE INFORMATION:

04/01/19	New Medical Coverage Guideline.
05/15/19	Revision to guideline; consisting of updating position statement, coding and references.
06/15/19	Revision to guideline; consisting of updating position statement.
01/15/20	Revision to guideline; consisting of updating the position statement.