PDL DRUG REVIEW

Proprietary Name: Vitrakvi®
Common Name: larotrectinib
PDL Category: Antineoplastics

Summary

Pharmacology/Usage: Larotrectinib, the active ingredient of Vitrakvi®, is a kinase inhibitor. Specifically, it is an inhibitor of the tropomyosin receptor kinases (TRK), TRKA, TRKB, and TRKC. In in vitro and in vivo tumor models, larotrectinib demonstrated anti-tumor activity in cells with constitutive activation of TRK proteins resulting from gene fusions, deletion of a protein regulatory domain, or in cells with TRK protein overexpression.

Indication: 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.

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.

There is no pregnancy category listed for this product; however, the risk summary indicates that based on literature reports in human subjects with congenital mutations leading to changes in TRK signaling, findings from animal studies, and its mechanism of action, Vitrakvi® can cause embryo-fetal harm when administered to a pregnant woman. There are no available data on use in pregnant women. Advise pregnant women of the potential risk to the fetus. Verify pregnancy status in females of reproductive potential prior to starting treatment. Advise female patients of reproductive potential to use effective contraception during treatment and for at least 1 week after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the final dose. The safety and efficacy of use in the pediatric population have been established.

Dosage Forms: The capsule and oral solution may be used interchangeably.

- Capsules: 25mg, 100mg. Do not chew or crush.
- Oral Solution: 20mg/ml. Store in refrigerator and discard any unused solution remaining after 90 days of first opening the bottle.

Recommended Dosage: Select patients for treatment based on the presence of a *NTRK* gene fusion in tumor specimens. An FDA-approved test for the detection of *NTRK* gene fusion is not currently available.

Adults/Pediatric patients with Body Surface Area (BSA) of ≥1.0m^2: Take 100mg PO BID, with or without food, until disease progression or until unacceptable toxicity.

Pediatric patients with Body Surface Area (BSA) of <1.0m^2: Take 100mg/m^2 PO BID, with or without food, until disease progression or until unacceptable toxicity.

Dose modifications may be required for grade 3 or 4 adverse reactions. Refer to the prescribing information for additional information. Dose adjustments are not required with renal impairment or with mild hepatic impairment. Reduce the starting dose of Vitrakvi® by 50% in patients with moderate to severe hepatic impairment.

Drug Interactions: Avoid concurrent use of strong CYP3A4 inhibitors with Vitrakvi®, including grapefruit or grapefruit juice. If coadministration cannot be avoided, reduce the Vitrakvi® dose by 50%. After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Vitrakvi® dose taken prior to starting the CYP3A4 inhibitor.

Avoid the concurrent use of strong CYP3A4 inducers with Vitrakvi®, including St. John's wort. If coadministration cannot be avoided, double the Vitrakvi® dose. After the inducer has been discontinued for 3 to 5 elimination half-lives, resume the Vitrakvi® dose taken prior to starting the CYP3A4 inducer.

Avoid the concurrent use of Vitrakvi® with sensitive CYP3A4 substrates. If coadministration cannot be avoided, monitor patients for increased adverse reactions of these drugs.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Vitrakvi®) for all grades. There was no placebo data in the prescribing information for comparison.* The most frequently reported adverse events included fatigue (37%), pyrexia (18%), edema peripheral (15%), nausea (29%), vomiting (26%), constipation (23%), diarrhea (22%), abdominal pain (13%), dizziness (28%), headache (14%), cough (26%), dyspnea (18%), nasal congestion (10%), increased weight (15%), arthralgia (14%), myalgia (14%), muscular weakness (13%), back pain (12%), pain in extremity (12%), decreased appetite (13%), hypertension (11%), and fall (10%). Laboratory abnormalities included increased ALT (45%), increased AST (45%), hypoalbuminemia (35%), increased alkaline phosphatase (30%), anemia (42%), and neutropenia (23%).

Neurotoxicity was reported in clinical trials with Vitrakvi®. Of the 176 patients treated with Vitrakvi®, neurologic adverse reactions of any graded occurred in 53% of patients, including grade 3 and grade 4 neurological adverse reactions in 6% and 0.6% of patients, respectively. Most of the neurologic adverse reactions (65%) occurred within the first 3 months of treatment. Grade 3 neurologic adverse reactions included delirium (2%), dysarthria (1%), dizziness (1%), gait disturbance (1%), and paresthesia (1%). Grade 4 encephalopathy occurred in 1 patient. Neurologic adverse reactions leading to dose modifications included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor (1%). Advise patients not to drive or operate heavy machinery if experiencing neurologic adverse reactions. Withhold or permanently discontinue treatment based on the severity.

Of the 176 patients treated with Vitrakvi® in a clinical trial, increased transaminases of any grade occurred in 45%, including grade 3 increased AST or ALT in 6% of patients. One patient experienced grade 4 increased ALT. The median time to onset of increased AST was 2 months and the median time to onset of increased ALT was 2 months. Increased AST and ALT leading to dose modifications occurred in 4% and 6% of patients, respectively. It is recommended to monitor liver function tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. Withhold or permanently discontinue Vitrakvi® based on the severity.

Contraindications: There are currently no contraindications listed with this product.

Manufacturer: Loxo Oncology, Inc

Analysis: The efficacy of Vitrakvi® was assessed in pediatric and adult patients with unresectable or metastatic solid tumors with a *NTRK* gene fusion who were enrolled in 1 of 3 multicenter, open-label, single-arm clinical trials. All patients were required to have progressed following systemic therapy for disease, if available, or would have

required surgery with significant morbidity for locally advanced disease. Identification of positive *NTRK* gene fusion status was prospectively determined in local laboratories using next generation sequencing or fluorescence in situ hybridization (FISH).

The assessment of efficacy was based on the first 55 patients with solid tumors with an *NTRK* gene fusion enrolled across the 3 clinical trials. The median age of patients was 45 years (range 4 months to 76 years), 78% were ≥18 years of age, 53% were male, 67% were white and 93% had an ECOG performance status of 0-1. In addition, 82% had metastatic disease and 18% had locally advanced, unresectable disease, while 98% had received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy.

The main efficacy outcome measures were overall response rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC) according to RECIST v1.1. Efficacy results can be seen in the table below, which was adapted from the prescribing information.

Endpoint	Vitrakvi®
ORR	N=55
Overall Response Rate	75%
Complete Response Rate	22%
Partial Response Rate	53%
DOR	N=41
Range, months	1.6+, 33.2+
% with duration ≥6 months	73%
% with duration ≥9 months	63%
% with duration ≥12 months	39%

+ denotes ongoing response

The following table, also adapted from the prescribing information, includes efficacy results by tumor type.

Tumor type	Patients (N=55)	ORR (%)	DOR, Range (months)
Soft tissue sarcoma	11	91%	3.6, 33.2+
Salivary glands	12	83%	7.7, 27.9+
Infantile fibrosarcoma	7	100%	1.4+, 10.2+
Thyroid	5	100%	3.7, 27.0+
Lung	4	75%	8.2, 20.3+
Melanoma	4	50%	1.9, 17.5+
Colon	4	25%	5.6
GI stromal tumor	3	100%	9.5, 17.3
Cholangiocarcinoma	2	SD, NE	NA
Appendix	1	SD	NA
Breast	1	PD	NA
Pancreas	1	SD	NA

NE-not evaluable; SD-stable disease; PD-progressive disease; + denotes ongoing response
NA-not applicable due to small # or lack of response;

Place in Therapy: Vitrakvi® is an oral kinase inhibitor 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. 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. In a single-arm study, Vitrakvi® was found to have a 75% overall response rate.

It is recommended that Vitrakvi® be placed on the Recommended Drug List as non-recommended and require prior authorization to confirm appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Vitrakvi [package insert]. Stamford, CT: Loxo Oncology, Inc; 2018.