CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210861Orig1s000
211710Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	210861 (capsules) & 211710 (oral solution)
PDUFA Goal Date	November 26, 2018
OSE RCM #	2017-2587 & 2589 for 210861; 2018-367 & 484 for 211710
Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader	Elizabeth Everhart, RN, MSN, ACNP
Division Director	Cynthia, LaCivita, Pharm.D.
Review Completion Date	August 23, 2108
Subject	Evaluation of Need for a REMS
Established Name	Larotrectinib
Trade Name	Vitrakvi
Name of Applicant	Loxo Oncology, Inc.
Therapeutic Class	Kinase inhibitor
Formulations	25 mg and 100 mg capsules; oral solution 20 mg/ml
Dosing Regimen	For adults: 100 mg orally twice daily; for pediatric patients: 100 mg/m2 orally twice daily with a maximum of 100 mg per dose

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Vitrakvi (larotrectinib) is necessary to ensure the benefits outweigh its risks. Loxo Oncology, Inc. (Loxo) submitted New Drug Applications (NDA) 210861 (capusles) and 211710 (oral solution) for larotrectinib with the proposed indication: for the treatment of adult and pediatric patients with unresectable locally advanced or metatstatic solid tumors with an activating Neurotropic Tropomyosin Receptor Kinase (NTRK) rearrangement or non-resistance mutation who have no satisfactory alternative treatment options or whose cancer has progressed following treatment. The serious risks associated with larotrectinib include neurotoxicity, hepatotoxicity, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Oncology Products 2 (DOP2) agree that a REMS is not necessary to ensure the benefits of larotrectinib outweigh its risks. The medical reviewer concluded that a high Overall Response Rate (ORR) was demonstrated in the clinical trial independent of age, tissue diagnosis, and NTRK isoform. The serious risks of larotrectinib are neurotoxicity, hepatotoxicity, and embryo-fetal toxicity. If the product is approved, these risks will be communicated in the Warnings and Precautions section of the labeling. To mitigate these risks, the proposed label will also include recommended dose modifications for these adverse reactions. Additionally, larotrectinib is metabolized predominantly by CYP3A4. Recommendations to avoid concomitant use of strong CYP3A4 inhibitors or inducers, as well as how to modify the dose of larotrectinib if co-administration cannot be avoided, will be conveyed in the Dosage and Administration section of the labeling.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Vitrakvi (larotrectinib) is necessary to ensure the benefits outweigh its risks. Loxo submitted New Drug Applications (NDA) 210861 (capsules) and 211710 (oral solution) for larotrectinib with the proposed indication for the treatment of adult and pediatric patients with unresectable locally advanced or metatstatic solid tumors with an activating Neurotropic Tropomyosin Receptor Kinase (NTRK) rearrangement or non-resistance mutation who have no satisfactory alternative treatment options or whose cancer has progressed following treatment. This application is under review in the DOP2. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Vitrakvi (larotrectinib), a new molecular entity,[a] is a kinase inhibitor, proposed for the treatment of adult and pediatric patients with unresectable locally advanced or metatstatic solid tumors with an activating NTRK rearrangement or non-resistance mutation who have no satisfactory alternative

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

treatment options or whose cancer has progressed following treatmentTropomyosin Receptor Kinases (TRK) is a receptor in the tyrosine kinase family that is activated by neurotrophine, a family of nerve growth factors. The TRK family includes TRKA, TRKB, and TRKC proteins, which are encoded by NTRK1, NTRK2, and NTRK3 genes, respectively. Larotrectinib is an inhibitor of tropomyosin receptor kinases (TRK). Larotrectinib is one of the first attempts at molecularly defined patient identification rather than traditional indications based on cancer location. TRK binds to neurotrophin growth factors, this group includes the following transmembrans proteins - TRKA, TRKB, and TRKC, which are encoded by the genes, NTRK1, NTRK2, and NTRK3. Laretrectinib turns off the signaling pathway that allows TRK fusion cancer to grow. Larotrectinib proposed as capsules of 25 mg and 100 mg and oral soultuion of 20 mg/ml. For adults, dosage is 100 mg orally twice daily. For pediatric patients, dosage 100 mg/m2 orally twice daily with a maximum of 100 mg per dose. The therapy is to continue until disease progression or intolerability of toxicities.[b] Larotrectinib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for larotrectinib relevant to this review:

- July 11, 2016: Breakthrough therapy designation granted under IND 121211.
- May 9, 2017: Orphan drug designation granted.
- November 17, 2017: pre-NDA meeting rolling review granted.
- March 26, 2018: NDA 210861 and 211710 submissions received.
- June 28, 2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for laretrectinib.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

TRK fusions are chromosomal abnormalities that occur when one of the NTRK genes (NTRK1, NTRK2, NTRK3) becomes connected to another, unrelated gene. This abnormalitiy results in uncontrolled TRK signaling that can lead to cancer. According to the presentation at the 2017 American Society of Clinical Oncology (ASCO) annual meeting,[1] the TRK fusion mutation occurs in about 0.5-1% of many common cancers but in greater than 90% of certain rare cancers, such as salivary gland cancer, a form of juvenile breast cancer, and infantile fibrosarcoma.[c] In pediatric non-brainstem glioblastoma, NTRK gene fusions accout for up to 47% of driver events.[2] TRK fusions can be identified through various diagnostic tests, including targeted next-generation sequencing (NGS), immune-histochemistry (IHC), polymerase chain reaction (PCR), and fluorescent in situ hybridization (FISH).

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Selective inhibition of TRK signaling may be beneficial among patients whose tumors vary in histologies, but share underlying oncogenic NTRK gene alterations. Larotrectinib is an oral and selective inhibitor of TRK, with activity against the TRK family of proteins TRKA, TRKB, and TRKC. Laretrectinib turns off the signaling pathway that allows TRK fusion cancer to grow. It is estimated 1500-5000 patients who are newly diagnosed with advanced cancer each year have a TRK fusion.[d] [3]

3.2 Description of Current Treatment Options

TRK fusions occur rarely but broadly in various adult and pediatric solid tumors, including appendiceal cancer, breast cancer, cholangiocarcinoma, colorectal cancer, gastrointestinal stromal tumor, infantile fibrosarcoma, lung cancer, mammary analogue secrectory carcinoma of the salivary gland, melanoma, pancreatic cancer, thyroid cancer, and various sarcomas.[4] Some of the currently available and not highly effective therapies include chemotherapies, steroids, and whole-brain radiation. The treatment varies depending on the type of solid tumor and may include radical surgery, oral and systemic chemotherapy, radiation, external beam radiation therapy and steroids. These treatments generally is not curative and additional therapy is needed. Currently there are no approved drug specifically targeting solid tumors with an activating NTRK rearrangement or non-resistant mutation. In settings where no treatment is available or significant morbidity exists, there remains a medical need for additional therapies.[5]

4 Benefit Assessment

The efficacy of larotrectinib was evaluated in pediatric and adult patients with unresectable locally advanced or metastatic solid tumors with an activating NTRK rearrangement or non-resistance mutation enrolled in one of 3 multicenter, open-label, single-arm clinical trials : Study LOXO-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431).[6] All patients were required to have progressed following systemic therapy, if available, or required surgery with significant morbidity for locally advanced disease. Identification of positive NTRK tumor status was prospectively determined using next generation sequencing (NGS) or fluorescence in situ hybridization (FISH) in local laboratories. The major efficacy outcome measures were overall responses rate (ORR) and duration of response (DOR), as determined by a blinded independent review committee (BIRC).

The assessment of efficacy was based on the first 55 patients with solid tumors with an activating NTRK rearrangement or non-resistance mutation enrolled across the 3 clinical trails. Baseline characteristic were: median age 45 years (range 0.3-76 years); 22%< 18 years of age; 53% male. Ninety-eight percent of pateints received prior treatment for their cancer, including surgery, radiotherapy, or systemic therapy. The most common cancers were salivary gland tumors (22%), soft tissue sarcoma (20%), infantile fibrosarcoma (13%), and thyroid cancer (9%). A total of 50 patients had NTRK gene fusions detected by NGS and 5 patients had NTRK gene fusions detected by FISH. Efficacy results are summarized in table 1.

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Table 1 Efficacy results for patients with NTRK fusion cancers

Efficacy parameter	**N=55**
Overall response rate (ORR) (95% CI)	**75%** (61, 85)
Complete response (CR)	22%
Partial response (PR)	51%
Duration of response (DOR)	**N=40**
Median (95% CI)	Not estimable (NE) (10.2, NE)
Range	1.6+, 33.2+ (in months, +denoates ongoing)
DOR>=6 months, n (%)	30 (75%)
DOR>= 12 months, n (%)	16 (40%)

Efficacy results by tumor type are summarized in table 2.

Table 2 Efficacy results by tumor type

Tumor type	Patients (n)	ORR n(%) 95% CI	DOR Range (month) ≥ 6 month
Soft tissue sarcoma	11	10 (91%) (59%, 100%)	3.6, 33.2+ 7(70%)
Salivary gland	12	10 (83%) (52%, 98%)	7.7, 27.9+ 10(100%)
Infantile fibrosarcoma	7	6 (86%) (42%, 100%)	1.6, 10.2+ 2 (33%)
thyroid	5	5(100%) (48%, na)	3.7, 27.0+ 4 (80%)
lung	4	3 (75%) (19%, 99)	8.2, 20.3+ 3(100%)
Melanoma	4	2 (50%) not evaluable	1.9, 17.5+ 1 (50%)
Colon	4	1 (25%) not evaluable	5.6 1 (100%)
GastroIntestinal stroma tumor (GIST)	3	3 (100%) (29%, na)	9.5, 17.3 3 (100%)

Responses were seen in patients regardless of age, tumor type, NTRK gene involved or NTRK gene fusion partner. In the pediatric sub-population (N=12), the ORR was 100%. Per medical reviewer, the clinical studies demonstrated high ORR independent of age, tissue diagnosis, and NTRK isoform with durable efficacy (median follow up 12.9 months and median duration of response have not reached yet).[7]

5 Risk Assessment & Safe-Use Conditions

Deaths: There were 3 deaths in the pooled safety database, one death in each study. The medical officer concluded that these deaths were not related to the use of larotrectinib.[8] One patient with bone sarcoma died of disease progression. One patient with colorectal cancere died of progressive disease/small intestinal obstruction. The last patient had central nervous tumor and died of cerebellar hemorrhage.

5.1 Neurotoxicity

Among the 176 patients who received larotrectinib, neurotoxicity occurred in 60% of patients, including grade 3 (6%) and grade 4 (0.6%). Grade 3 neurologic adverse reactions included delirium (2%), dysarthria (1%), dizziness (1%), gait disturbance (1%), and paresthesia (1%). Grade 4 encephalopathy (0.6%) occurred in a single patient. Neurolotoxicity leading to dose modification included dizziness (3%), gait disturbance (1%), delirium (1%), memory impairment (1%), and tremor (1%).

The label will advise patients and caretakers of these risks and will further advise patients not to drive or operate hazardous machinery if they are experiencing neurotoxicity. Further recommendations for dose reductions and permanent discontinuation will also be included in the label.

5.2 Hepatotoxicity

Among the 176 patients who received larotrectinib, hepatotoxicity occurred in 44%, including grade 3 increased aspartate aminotransferase (AST) or alanine aminotransferase (ALT) in 6% of patients. No cases met Hy's Law criteria.[9] The median time to increased AST or ALT was 3 months. Increased AST or ALT led to permanent discontinuation in 2% of pateints.

The label will recommend monitoring of liver tests, including ALT and AST, every 2 weeks during the first month of treatment, then monthly thereafter, and as clinically indicated. The label will further recommend that larotectinib should be withheld or permanently discontinued , based on the severity; if withheld, the dose should be reduced when resumed.

5.3 Embryo-fetal toxicity

Based on its mechanism of action and findings from animal studies, larotrectinib can cause embryo-fetal harm when administered to a pregnant woman. Administration of larotrectinib to pregnant rats and rabbits during the period of organogenesis resulted in malformations at maternal exposures that were approximately 0.6 and 0.3 times, respectively, those observed at the clinical dose of 100 mg twice daily.

If approved, the label will advise women of the potential risk to a fetus and will further advise females of reproductive potential to use an effective method of contraception during treatment and for (b) (4) after the final dose of larotrectinib.

6 Expected Postmarket Use

It is expectd that oncologists and pediatric oncologists will be the primary prescribers and the use will be primarily in the outpatient setting.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for larotrectinib beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of larotrectinib on the basis of the efficacy and safety information currently available.[10] When evaluating factors of whether a REMS is necessary to ensure that the benefits outweight the risk of larotrectinib, DRISK considers patient population size, seriousness of the disease, expected benefit of the drug, the expected duration of treatment, the seriousness of known or potential adverse reactions, and whether the drug is an NME.

TRK fusions occur rarely but broadly in various adult and pediatric solid tumors. The TRK fusion mutation occurs in about 0.5-1% of many common cancers but in greater than 90% of certain rare cancers, such as salivary gland cancer, a form of juvenile breast cancer, and infantile fibrosarcoma.[e] In pediatric non-brainstem glioblastoma, NTRK gene fusions accout for up to 47%. It is estimated 1500-5000 patients who are newly diagnosed with advanced cancer each year have a TRK fusion. The currently available and not highly effective therapies include chemotherapies, steroids and whole-brain radiation. Patients with locally advanced or metastatic solid tumors who harboring an NTRK gene fusion have dismal outcomes. There remains a clear medical need to develop a new therapy for the treatment of these patient.

The medical reviewer concluded that high ORR was demonstrated in the clinical trial with independence of age, tissue diagnosis, and NTRK isoform. The duration of response (DOR) is durable with median time of 12.9 months followup and median DOR has not yet been reached.

The serious risks of larotrectinib are neurotoxicity, hepatotoxicity, and embryo-fetal toxicity. If the product is approved, these risks will be communicated in the Warnings and Precautions section of the labeling. To mitigate these risks, the proposed label will also include recommended dose modifications for these adverse reactions. Additionally, larotrectinib is metabolized predominantly by CYP3A4. The recommendation to avoid concomitant use of strong CYP3A4 inhibitors or inducers will be conveyed in Dosage and Administration section of the labeling;if co-administration cannot be avoided, it will be recommended that the dose of larotrectinib dose is modified.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable. DRISK's recommendation is that a REMS is not necessary for larotrectinib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety

[e] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Hyman DM, Laetsch TW, et al. presentation at 2017 ASCO annual meeting , #ASCO17, Hyman, LBA2501

[2] Kohtskaya YB, et al. Targeting TRK family proteins in cancer. Pharmacology & Therapeutics. 2017; 173: 58-66

[3] Hyman DM, Laetsch TW, et al. presentation at 2017 ASCO annual meeting , #ASCO17, Hyman, LBA2501

[4] Drilon A, Laetsch TW, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018; 378: 731-739

[5] Marcus L, Draft clinical review, August 23, 2018

[6] Proposed prescribing information of larotrectinib, updated August 16, 2018

[7] Marcus L and Donoghue M, the mid-cycle presentation of larotrectinib, June 15, 2018

[8] Marcus L and Donoghue M, the mid-cycle presentation of larotrectinib, June 15, 2018

[9] Marcus L and Donoghue M, the mid-cycle presentation of larotrectinib, June 15, 2018

[10] Marcus L , Draft clinical review, Augest 23, 2018

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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I concur

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