CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219304Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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	219304
PDUFA Goal Date	February 17, 2025
Nexus TTT #	2024-9864, 2024-9866
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
Team Leader	Naomi Boston, Pharm.D.
Acting Division Director	Laura Zendel, Pharm.D.
Review Completion Date	February 11, 2025
Subject	Evaluation of Need for a REMS
Established Name	Vimseltinib
Trade Name	Romvimza
Name of Applicant	Deciphera Pharmaceuticals, LLC
Therapeutic Class	kinase inhibitor
Formulation(s)	14 mg, 20 mg, 30 mg capsules
Dosing Regimen	vimseltinib 30 mg orally twice weekly with a minimum of 72 hours between doses

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Romvimza (vimseltinib) is necessary to ensure the benefits outweigh its risks. Deciphera Pharmaceuticals, LLC submitted a New Drug Application (NDA) 219304 for vimseltinib with the proposed indication for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT). The FDA approved indication will be for the treatment of adult patients with symptomatic TGCT for which surgical resection will potentially cause worsening functional limitation or severe morbidity. The serious risks associated with vimseltinib include hepatotoxicity, embryo-fetal toxicity, allergic reactions to FD&C Yellow No.5 (tartrazine) and No. 6 (Sunset Yellow FCF), and increased creatinine without affecting renal function. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and Division of Oncology 3 (DO3) agree that a REMS is not necessary to ensure the benefits of vimseltinib outweigh its risks. The efficacy of vimseltinib was supported by study MOTION, in which the vimseltinib group had an overall response rate of 40%. Labeling that includes warnings and precautions and Medication Guide will be used to communicate the serious risk of hepatotoxicity. The other serious risks including embryo-fetal toxicity, allergic reactions to FD&C Yellow No.5 (tartrazine) and No. 6 (Sunset Yellow FCF), and increased creatinine without affecting renal function will also be communicated in the warnings and precautions section of the label and a Medication Guide. None of the risks associated with vimseltinib rise to the level of a boxed warning, including the risk of hepatotoxicity. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with vimseltinib.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Romvimza (vimseltinib) is necessary to ensure the benefits outweigh its risks. Deciphera Pharmaceuticals, LLC submitted a New Drug Application (NDA) 219304 for vimseltinib with the proposed indication for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT).[1] This application is under review in the Division of Oncology 3 (DO3). The applicant did not submit a proposed REMS or risk management plan.

2. Background

2.1. Product Information

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

Romvimza (vimseltinib), a NME, is proposed for the treatment of adult patients with symptomatic TGCT. Vimseltinib is a kinase inhibitor that inhibits colony-stimulating factor 1 receptor (CSF1R). In vitro, vimseltinib inhibited CSF1R autophosphorylation, signaling induced by colony stimulating factor 1 (CSF1) ligand binding, and proliferation of cells expressing CSF1R. Vimseltinib is proposed to be supplied as 14 mg, 20 mg, and 30 mg capsules. The proposed dosing regimen is vimseltinib 30 mg orally twice weekly with a minimum of 72 hours between doses.[b] Vimseltinib is not currently approved in any jurisdiction. Vimseltinib received fast track designation.

2.2. Regulatory History

The following is a summary of the regulatory history for vimseltinib NDA 219304 relevant to this review:

- 9/28/2021: Fast track designation granted
- 06/17/2024: NDA 219304 submission for the treatment of adult patients with symptomatic TGCT received
- 10/07/2024: 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 vimseltinib

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

TGCT is a rare, non-malignant tumor associated with pain, stiffness and functional impairment of the joints and limbs.[2,3] Two subgroups of this disease include localized type which affects smaller joints in the hand and feet and diffuse type which is more common in lower extremity (knee) and large joints.[3,4] The annual incidence of localized and diffuse TGCT in the United States is 9.2 cases per million and 1.8 cases per million, respectively.[3,5,c] TGCT is caused by dysregulation of the CSF1 gene which results in overproduction of CSF1 and recruitment of CSF1R-dependent inflammatory cells into the affected joint. Patients are usually diagnosed between the ages of 35 and 50 years old, and most often presents with pain and swelling at the affected joint.[5,6] Due to the slow growing nature of the tumor, symptoms are minimal at first. The tumors often expand in the intra-articular space of the joints and surrounding

[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 (A): The estimated size of the population likely to use the drug involved.*

tissues, which can lead to severe pain, swelling, and reduced range of motion of the affected limb(s). While TGCT is not fatal, it may cause substantial morbidity in patients.[4,d]

3.2. Description of Current Treatment Options

Surgery remains the recommended treatment for all forms of TGCT, when feasible.[5] Localized TGCT can generally be surgically removed, but removal of diffuse TGCT may be challenging because the diffuse nature of the lesions may make full excision difficult. The recurrence rates for localized TGCT and diffuse TGCT after surgery are approximately 10% and up to 55%, respectively.

Turalio (pexidartinib), a tyrosine kinase inhibitor that targets CSF1R, KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication (ITD) mutation, was approved by the FDA in 2019 for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery.[7] Pexidartinib has a boxed warning for hepatotoxicity and a REMS with elements to assure safe use (ETASU) to mitigate the risk of serious and potentially fatal liver injury. Hepatotoxicity including liver failure and life-threatening vanishing bile duct syndrome (VBDS), ductopenia, and symptomatic cholestasis (including severe pruritis) has occurred in patients treated with pexidartinib and can occur despite monitoring and prompt drug cessation. Mild, reversible aspartate aminotransferase (AST) / alanine aminotransferase (ALT) elevation occurs in a predictable, dose- dependent manner and has been reported for other agents targeting the CSF-1/CSF1R pathway.[3] However, the mechanism of cholestatic hepatotoxicity with pexidartinib is unknown and its occurrence cannot be predicted. The Turalio REMS consists of a communication plan, ETASU, an implementation system, and a timetable for submission of assessments of the REMS. The ETASU requires that healthcare providers have training and are specially certified, pharmacies that dispense the drug are specially certified, and each patient using Turalio is subject to certain monitoring and is enrolled in a registry. The other serious risks associated with pexidartinib include embryo-fetal toxicity and the potential for increased adverse events when pexidartinib is taken with a high-fat meal.[7]

Please refer to the DO3 multi-disciplinary review and evaluation (draft) for vimseltinib for a detailed clinical review on treatment armamentarium relevant to the proposed indication.

4. Benefit Assessment

The pivotal trial MOTION (NCT 05059262) supporting this application for efficacy and safety consisted of a Phase 3, double blind, multicenter, randomized, placebo controlled study which evaluated vimseltinib in patients with TGCT for whom surgical resection may cause worsening functional limitation or severe morbidity.[1,5] Patients (N=123) were randomized to vimseltinib 30 mg orally twice weekly for 24 weeks

[d] 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.*

(N=83) or placebo (N=40). The primary endpoint was overall response rate (ORR) as assessed by blinded independent radiological review (IRR) per Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 at Week 25. The vimseltinib treatment group had an ORR of 40% (95% CI 29 to 51) and the placebo group had an ORR of 0% (95% CI 0 to 9), p<0.0001. The median duration of response was not reached in the vimseltinib group (range 2.5+ to 19.4+ months).

Secondary endpoints included ORR as assessed using tumor volume score (TVS), mean change from baseline in active range of motion (ROM) of the affected joint at Week 25 measured by goniometry assessments, change from baseline in the Patient-Reported Outcomes Measurement Information System-Physical Function (PROMIS-PF) 15-item score (upper and lower extremity items), and response of at least a 30% improvement in the mean Brief Pain Inventory (BPI) Worst Pain numeric rating scale (NRS) score without a 30% or greater increase in narcotic analgesic use. The ORR by TVS was 67% in the vimseltinib group (95% CI 56 to 77) and 0% in the placebo group, p <0.0001. The analysis of the active ROM demonstrated a difference in least squares means of 14.6% (95% CI 4.0 to 25.3), p=0.0077. The difference in least squares means for PROMIS-PF was 3.3 points (95% CI 1.4 to 5.2), p=0.0007. The difference in responder rate for BPI-30 response was 26.2% (95% CI 9.5 to 42.8), p=0.0056. The clinical reviewer concluded that the MOTION study demonstrated a clinically meaningful and durable response in patients who received vimseltinib compared to placebo.[e]

5. Risk Assessment & Safe-Use Conditions

The safety of vimseltinib was evaluated in a Phase 3 clinical trial MOTION.[1,5,f] In the safety population, 83 patients received vimseltinib and 39 patients received placebo. However, the pooled safety population for the serious risks described in labeling reflects exposure to vimseltinib in 83 patients with TGCT enrolled in the double-blind portion of the MOTION trial and 135 patients with TGCT or solid tumors in other Phase 1/2 clinical trials. Discontinuation due to a treatment emergent adverse event (TEAE) occurred in 4.8% in the vimseltinib group and 0% in the placebo group. Common adverse reactions including laboratory abnormalities reported with vimseltinib were increased AST, periorbital edema, fatigue, rash, increased cholesterol, peripheral edema, face edema, decreased neutrophils, decreased leukocytes, pruritus, and increased ALT.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

The serious risks[g] associated with vimseltinib which include hepatotoxicity, embryo-fetal toxicity, allergic reactions to FD&C Yellow No.5 (tartrazine) and No. 6 (Sunset Yellow FCF), and increased creatinine without affecting renal function are summarized in the sections below.

5.1. Hepatotoxicity

Due to cases of serious and fatal liver injury having occurred with the use of pexidartinib, hepatotoxicity was reviewed closely for vimseltinib. In the clinical trial setting, serious and fatal liver injury has not been observed with vimseltinib. No patients receiving vimseltinib had drug-induced liver injury (DILI) and no cases met the criteria for Hy's law.[3] In the MOTION study, increased ALT occurred in 24% of patients receiving vimseltinib, with no Grade 3 or 4 increased ALT reported. Increased AST occurred in 92% of patients receiving vimseltinib, with no Grade 3 or 4 increased AST reported. There were no patients who experienced increased bilirubin >ULN and < 2 x ULN. In addition, in the pooled safety population, an adverse event of Grade 3 increased ALT and Grade 3 increased AST were reported in 1% and 3% of patients, respectively.

The proposed label recommends avoiding vimseltinib in patients with pre-existing increased serum transaminases; total bilirubin or direct bilirubin (>ULN); or active liver or biliary tract disease, including alkaline phosphatase (ALP). It recommends monitoring liver tests, including AST, ALT, total bilirubin, direct bilirubin, ALP and gamma-glutamyl transferase (GGT) prior to initiation of vimseltinib, twice a month for the first two months and once every 3 months for the first year of therapy and as clinically indicated thereafter. Healthcare providers are instructed to withhold and reduce the dose, or permanently discontinue vimseltinib based on the severity of the hepatotoxicity. Recommendations for dosage modifications for hepatotoxicity are addressed in section 2 of the label. If approved, this risk will be communicated in the warnings and precautions section of the label and a medication guide.

5.2. Embryo-Fetal Toxicity

Vimseltinib can cause fetal harm based on animal studies and the mechanism of action of the drug. Vimseltinib has been reported to cause fetal structural abnormalities in female rats at exposures that were at least 3 times the recommended dose based on area under the curve (AUC). No clinical data is available with vimseltinib in pregnancy in humans. The risk of embryo-fetal toxicity is proposed to be included in a Medication Guide and the warnings and precautions section of the label. The proposed label states to advise pregnant women on the potential risk to the fetus. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting vimseltinib and that effective contraception be used during treatment and for 1 month after the last dose. In

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

addition, in males with female partners of reproductive potential it is recommended that effective contraception be used during treatment and for 1 month after the last dose.

5.3. Allergic Reactions to FD&C Yellow No.5 (Tartrazine) and No. 6 (Sunset Yellow FCF)

Vimseltinib 20 mg capsule contains FD&C Yellow No. 5 (tartrazine) which may cause allergic reactions including bronchial asthma in certain susceptible patients. FD&C Yellow No. 5 (tartrazine) sensitivity is frequently seen in patients who also have aspirin sensitivity. In addition, vimseltinib 14 mg and 20 mg capsules contain FD&C Yellow No.6 (Sunset Yellow FCF) which may cause allergic reactions. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.4. Increased Creatinine without Affecting Renal Function

Vimseltinib may increase serum creatinine without affecting renal function. In the MOTION study, serum creatinine increased (mean increase of 19 µmol/L) and reached a maximum mean increase by 10.4 weeks compared to baseline. The increases in creatinine reversed upon vimseltinib discontinuation. The increases in serum creatinine may be due to inhibition of renal tubular secretion transporters. The proposed label recommends during vimseltinib treatment use alternative measures that are not based on serum creatinine to assess renal function. If approved, this risk will be communicated in the warnings and precautions section of the label.

6. Expected Postmarket Use

If approved, vimseltinib is likely to be prescribed in an ambulatory care setting by medical oncologists who treat sarcomas or diagnose symptomatic TGCT. These healthcare providers likely have experience with other therapies including pexidartinib that have a risk of hepatotoxicity.

7. Risk Management Activities Proposed by the Applicant

The Applicant proposed risk management activities for vimseltinib including pharmacovigilance and labeling. The Applicant is also proposing (b) (4)

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of vimseltinib on the basis of the efficacy and safety information currently available. Vimseltinib is a kinase inhibitor and is an additional treatment option

for adult patients with symptomatic TGCT for which surgical resection will potentially cause worsening functional limitation or severe morbidity.

The efficacy of vimseltinib was supported by study MOTION, in which the vimseltinib group had an ORR of 40%. The serious risk associated with vimseltinib of hepatotoxicity will be communicated in the warnings and precautions section of the label and a Medication Guide. The other serious risks including embryo-fetal toxicity, allergic reactions to FD&C Yellow No.5 (tartrazine) and No. 6 (Sunset Yellow FCF), and increased creatinine without affecting renal function will also be communicated in the warnings and precautions section of the label and a Medication Guide. None of the risks associated with vimseltinib rise to the level of a boxed warning, including the risk of hepatotoxicity.

DRM and DO3 agree that a REMS is not necessary to ensure that the benefits outweigh the risks for vimseltinib. The following information is used to support this conclusion:

1. In the MOTION study, no cases of serious or fatal liver injury have been observed in patients treated with vimseltinib. Elevations in ALT occurred in 11% of patients, elevations in AST occurred 23% of patients, and elevations in bilirubin did not occur in any patients. No patients receiving vimseltinib had DILI and no cases met the criteria for Hy's law. The risk of hepatotoxicity associated with vimseltinib did not rise to the level of a boxed warning. In contrast, in the registrational trial for pexidartinib, ENLIVEN (NCT 02371369), serious liver injury was reported in 5% of patients. In the overall development program of pexidartinib, there were 2 cases of irreversible cholestatic liver injury, one patient with advanced cancer and ongoing liver toxicity died and one patient with a confirmed case of VBDS required a liver transplant. In addition, in the first 609 patients who received pexidartinib under the REMS program there were 2 cases of VBDS. Instructions for avoiding vimseltinib in patients with pre-existing increased serum transaminases; total bilirubin or direct bilirubin (>ULN); or active liver or biliary tract disease, including ALP are planned for inclusion in the labeling. Also planned for inclusion are instructions for monitoring liver tests, including AST, ALT, total bilirubin, direct bilirubin, ALP and GGT prior to initiation of vimseltinib, twice a month for the first two months and every three months for the first year of treatment, then as clinically indicated. The proposed labeling contains recommendations to withhold, dose reduce or permanently discontinue vimseltinib based on the severity of the hepatotoxicity.
2. The need for a Boxed Warning or other risk mitigation such as a REMS may be reassessed if there are post-marketing reports of serious or fatal liver injury with vimseltinib. DO3 is recommending a post-marketing requirement (PMR) for a registry with comprehensive safety analysis to evaluate the potential risk of serious hepatotoxicity.

TGCT is a rare, non-malignant tumor associated with pain, stiffness and functional impairment of the joints and limbs. Two subgroups of this disease include localized type which affects smaller joints in the hand and feet and diffuse type which is more common in lower extremity (knee) and large joints. The annual incidence of localized and diffuse TGCT in the United States is 9.2 cases per million and 1.8 cases per million, respectively. While TGCT is not fatal, it may cause substantial morbidity in patients. If approved, based on the available data and the review team's evaluation of the benefit-risk profile associated with vimseltinib for the treatment of adult patients with symptomatic TGCT for which surgical resection will potentially cause worsening functional limitation or severe morbidity, the DRM

and DO3 recommendation is that a REMS is not necessary to ensure the benefits outweigh the risks as the risks can be adequately communicated in labeling. No cases of serious and fatal liver injury have been observed in patients treated with vimseltinib. The REMS Oversight Committee (ROC) was informed on January 29, 2025 and agreed with the review team's determination that a REMS is not necessary to mitigate hepatotoxicity associated with vimseltinib. The review team could not fully rule-out the risk for hepatotoxicity with vimseltinib, therefore, the proposed labeling includes warnings and precautions and a Medication Guide to communicate the serious risk of hepatotoxicity. The proposed labeling includes recommendations for management of hepatotoxicity, as well as recommendations for monitoring and dosage modifications for hepatotoxicity. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with vimseltinib, as well as other therapies used in the treatment of symptomatic TGCT. Additionally, postmarketing requirements for vimseltinib include a registry study for hepatotoxicity and a study to evaluate vimseltinib in participants with moderate hepatic impairment, among others.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for vimseltinib to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. Appendices

10.1. References

[1] Proposed prescribing information for vimseltinib as currently edited by FDA, last accessed February 7, 2025.

[2] Boston N. Division of Risk Management NME review for pexidartinib NDA 211810, August 1, 2019.

[3] Stundon J, Doros L, Mushti S, Song C. Division of Oncology 3 (DO3). Vimseltinib NDA 219304. Mid-Cycle Meeting, clinical and statistics reviewer slides. September 30, 2024.

[4] Stacchiotti S, Durr HR, Schaefer IM, et al. Best clinical management of tenosynovial giant cell tumour (TGCT): A consensus paper from the community of experts. *Cancer Treat Rev*. 2023;112:102491.

[5] Romvimza (vimseltinib) NDA 219304 multi-disciplinary review and evaluation. Last accessed February 7, 2025.

[6] Oncologic Drugs Advisory Committee (ODAC) Briefing Document. Pexidartinib NDA 211810. Oncologic Drugs Advisory Committee Meeting. May 14, 2019.

[7] Turalio (pexidartinib) package insert. Basking Ridge, NJ: Daiichi Sankyo, Inc., 2025 January.

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