CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217700Orig1s000
218033Orig1s000

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	217700, 218033
PDUFA Goal Date	April 30, 2024
Nexus TTT #	2023-5160, 2023-5163, 2023-5214, 2023-5219
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Laura Zendel, Pharm.D.
Review Completion Date	April 22, 2024
Subject	Evaluation of Need for a REMS
Established Name	tovorafenib
Trade Name	Ojemda
Name of Applicant	Day One Biopharmaceuticals, Inc.
Therapeutic Class	kinase inhibitor
Formulation(s)	100 mg tablet (NDA 217700), 25 mg/mL oral suspension (NDA 218033)
Dosing Regimen	tovorafenib 380 mg/m^2 orally once weekly (the maximum recommended dosage is 600 mg orally once weekly)

Table of Contents

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 Ojemda (tovorafenib) is necessary to ensure the benefits outweigh its risks. Day One Biopharmaceuticals, Inc. submitted a New Drug Application (NDA) 217700 (tovorafenib 100 mg tablets) and NDA 218033 (tovorafenib 25 mg/mL oral suspension) for tovorafenib with the proposed indication for the treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation. The serious risks associated with tovorafenib include hemorrhage, skin toxicity including photosensitivity, hepatotoxicity, effect on growth, embryo-fetal toxicity, and NF1 associated tumors. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and Division of Oncology 2 (D02) agree that a REMS is not necessary to ensure the benefits of tovorafenib outweigh its risks. The efficacy of tovorafenib was supported by the FIREFLY-1 study Arm 1, in which the tovorafenib group had an overall response rate of 51%. DO2 recommends accelerated approval based on the currently available data. The serious risks associated with tovorafenib of hemorrhage, skin toxicity including photosensitivity, hepatotoxicity, effect on growth, embryo-fetal toxicity, and NF1 associated tumors will be communicated in the warnings and precautions section of the label. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with tovorafenib.

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] Ojemda (tovorafenib) is necessary to ensure the benefits outweigh its risks. Day One Biopharmaceuticals, Inc. submitted a New Drug Application (NDA) 217700 (tovorafenib 100 mg tablets) and NDA 218033 (tovorafenib 25 mg/mL oral suspension) for tovorafenib with the proposed indication for the treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.[1] This application is under review in the Division of Oncology 2 (D02). The applicant did not submit a proposed REMS or risk management plan.

2. Background

2.1. Product Information

Ojemda (tovorafenib), an NME, is a kinase inhibitor, proposed for the treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation. Tovorafenib is a Type II rapidly accelerated fibrosarcoma (RAF) kinase inhibitor of mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases. Tovorafenib is

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

proposed to be supplied as a 100 mg tablet (NDA 217700) and 25 mg/mL oral suspension (NDA 218033). The proposed dosing regimen is tovorafenib 380 mg/m^2 orally once weekly (the maximum recommended dosage is 600 mg orally once weekly) until disease progression or intolerable toxicity.[b] Tovorafenib is not currently approved in any jurisdiction. Tovorafenib was designated as an orphan product and as breakthrough therapy. If approved, the indication will be approved under accelerated approval based on response rate and duration of response.

2.2. Regulatory History

The following is a summary of the regulatory history for tovorafenib NDA 217700 and NDA 218033 relevant to this review:

- 08/31/2020: Breakthrough therapy designation granted for the treatment of pediatric patients with LGG harboring an activating RAF alteration that has progressed after one or more therapies
- 09/24/2020: Orphan drug designation granted
- 08/31/2023: NDA 217700 and NDA 218033 submission for the treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric LGG harboring a BRAF fusion or rearrangement, or BRAF V600 mutation received
- 01/31/2024: 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 tovorafenib

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Low grade gliomas are the most common cause of central nervous system tumors in children.[2,3] The annual incidence of pediatric LGG in the United States is 1000 to 1600 cases.[c] Pediatric LGG encompass different histologies such as astrocytic, oligodendroglial, and mixed glial-neuronal histology.[2,4] Most tumors harbor a single identifiable driver alteration, with BRAF alterations occurring in up to 70% of pediatric LGG. The KIAA1549:BRAF fusion is the most commonly identified alteration found in approximately 35% of tumors and the BRAF V600E mutation is found in approximately 15% of tumors.[4,5] Patients with LGG rarely develop malignant transformation and the 10-year overall survival rate is greater than 90%.[6,d]

[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.*

[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.*

3.2. Description of Current Treatment Options

The treatment of pediatric LGG includes surgical resection, chemotherapy and/or radiation therapy.[2] Initial treatment for pediatric LGG includes surgical resection. Treatment of progressive or recurrent tumors without a targetable genomic alteration includes chemotherapy as front-line adjuvant treatment. There are no specific therapies approved by the FDA for the treatment of pediatric LGG with wild-type BRAF fusions. Recently, the kinase inhibitor Tafinlar (dabrafenib) in combination with the kinase inhibitor Mekinist (trametinib) was approved by the FDA for the treatment of pediatric patients 1 year of age and older with LGG with a BRAF V600E mutation who require systemic therapy.[7,8] Dabrafenib and trametinib received accelerated approval in 2022 and full approval in 2023. The serious risks associated with dabrafenib include new primary malignancies, tumor promotion in BRAF wild-type tumors, hemorrhage, cardiomyopathy, uveitis, serious febrile reactions, serious skin toxicities, hyperglycemia, glucose-6-phosphate dehydrogenase deficiency, risks associated with combination treatment, hemophagocytic lymphohistiocytosis, and embryo-fetal toxicity. The serious risks associated with trametinib include new primary malignancies, hemorrhage, colitis and gastrointestinal perforation, venous thromboembolic events, cardiomyopathy, ocular toxicities, interstitial lung disease/pneumonitis, serious febrile reactions, serious skin toxicities, hyperglycemia, risks associated with combination treatment, hemophagocytic lymphohistiocytosis, and embryo-fetal toxicity. Dabrafenib and trametinib do not have a boxed warning in their respective labels and did not require a REMS. Please refer to D02's Assessment Aid (draft) for tovorafenib for a detailed clinical review on treatment armamentarium relevant to the proposed indication.

4. Benefit Assessment

The pivotal trial FIREFLY-1 (NCT 04775485) supporting this application for efficacy consisted of a Phase 2, multicenter, open-label study.[1,2] In the FIREFLY-1 study in Arm 1, there were 76 patients with relapsed or refractory pediatric LGG harboring a BRAF alteration. Patients received tovorafenib approximately 420 mg/m^2 orally once weekly (range: 290 to 476 mg/m^2) according to body surface area with a maximum dose of 600 mg until disease progression or unacceptable toxicity. The endpoints included overall response rate (ORR) by independent review based on RAPNO-LGG (Response Assessment in Pediatric Neuro-Oncology) criteria and duration of response (DOR). The tovorafenib treatment group had an ORR of 51% (95% CI 40% to 63%). The median DOR was 13.8 months in the tovorafenib group (95% CI 11.3 to not estimable). The FDA clinical reviewer recommended accelerated approval based on the currently available data.[e] The FDA clinical reviewer stated the submitted evidence meets the statutory evidentiary standard for accelerated approval through demonstration of an effect on an endpoint reasonably likely to predict clinical benefit.

[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.*

5. Risk Assessment & Safe-Use Conditions

The safety of tovorafenib was evaluated in a Phase 2 clinical trial FIREFLY-1 (NCT 04775485).[1,2,f] In the safety population, 137 patients received tovorafenib in FIREFLY-1 Arms 1 and 2. However, the safety population for the serious risks described in labeling reflects exposure to tovorafenib taken orally once weekly at a dose based on body surface area in all patients from FIREFLY-1 (140 patients) with relapsed or refractory pediatric LGG or advanced solid tumors harboring a RAF alteration and 32 adult patients from Study C28001 investigating tovorafenib in advanced solid tumors including melanoma who received a flat dose of 600 mg until disease progression or intolerable toxicity. Discontinuation due to an adverse reaction occurred in 7% of patients exposed to tovorafenib. Common adverse reactions reported with tovorafenib included rash, hair color changes, fatigue, viral infection, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea, dermatitis acneiform and upper respiratory tract infection. The most common Grade 3 or 4 laboratory abnormalities included decreased phosphate, decreased hemoglobin, increased creatinine phosphokinase, increased alanine aminotransferase (ALT), decreased albumin, decreased lymphocytes, decreased leukocytes, increased aspartate aminotransferase (AST), decreased potassium, and decreased sodium.

Four deaths due to an adverse event were reported in the FIREFLY-1 study in patients exposed to tovorafenib.[2] The Applicant indicated the causes of death due to an adverse event included brain death, hydrocephalus, disease progression, and tumor hemorrhage.

The serious risks[g] associated with tovorafenib which include hemorrhage, skin toxicity including photosensitivity, hepatotoxicity, effect on growth, embryo-fetal toxicity, and NF1 associated tumors are summarized in the sections below**.**

5.1. Hemorrhage

Section 5.1 of the draft labeling states that tovorafenib can cause hemorrhage, including major hemorrhage. Hemorrhagic events occurred in 37% of patients, including epistaxis in 26% of patients and intratumoral hemorrhage in 9% of patients. Serious events of bleeding occurred in 5% of patients receiving tovorafenib, with Grade 5 tumor hemorrhage reported in 0.6% of patients (n=1).

The proposed label states to advise patients and caregivers of the risk of hemorrhage during treatment with tovorafenib. The proposed label recommends to monitor for signs and symptoms of hemorrhage and evaluate as clinically indicated and to withhold and resume at reduced dose upon improvement, or

[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.*

[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.

permanently discontinue based on severity. Dose modifications for tovorafenib will be addressed in section 2 of the proposed label. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2. Skin Toxicity Including Photosensitivity

Section 5.2 of the draft labeling states that tovorafenib can cause rash, including maculopapular rash and photosensitivity. An adverse event of rash occurred in 67% of patients receiving tovorafenib, with Grade 3 rash reported in 12% of patients. An adverse event of dermatitis acneiform occurred in 26% of patients receiving tovorafenib, with Grade 3 dermatitis acneiform reported in 0.6% of patients (n=1). The proposed label states to monitor for new or worsening skin reactions. The proposed label also states to consider dermatologic consultation and initiate supportive care as clinically indicated and to withhold, reduce the dose, or permanently discontinue tovorafenib based on severity of adverse reaction.

An adverse event of photosensitivity occurred in 12% of patients receiving tovorafenib, with Grade 3 photosensitivity reported in 0.6% of patients (n=1). The proposed label states to use precautionary measures against ultraviolet exposure such as use of sunscreen, sunglasses, and/or protective clothing during treatment with tovorafenib. The proposed label recommends to withhold, reduce the dose, or permanently discontinue tovorafenib based on severity of adverse reaction. If approved, these risks will be communicated in the warnings and precautions section of the label.

5.3. Hepatotoxicity

Section 5.3 of the draft labeling states that tovorafenib can cause hepatotoxicity. An adverse event of increased ALT occurred in 42% of patients and increased AST occurred in 74% patients receiving tovorafenib, with Grade 3 increased ALT reported in 4% of patients and Grade 3 increased AST reported in 2% of patients. An adverse event of increased bilirubin occurred in 23% of patients receiving tovorafenib, with Grade 3 increased bilirubin reported in 0.6% of patients (n=1). The proposed label states to monitor liver function tests, including ALT, AST and bilirubin, before initiation of tovorafenib, one month after initiation and then every three months thereafter and as clinically indicated. It recommends to withhold and resume at the same or reduced dose upon improvement, or permanently discontinue tovorafenib based on the severity. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.4. Effect on Growth

Section 5.4 of the draft labeling states that tovorafenib can cause reductions in growth velocity. In FIREFLY-1, a treatment-emergent adverse effects on growth occurred in 15% of patients 18 years of age or younger receiving tovorafenib, with Grade 3 effects on growth reported in 5% of patients. The proposed label recommends to routinely monitor patient growth during treatment with tovorafenib. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.5. Embryo-Fetal Toxicity

Tovorafenib may cause fetal harm based on the mechanism of action of the drug and animal studies. Tovorafenib was embryo lethal in rats at doses approximately 0.8-fold the human exposure at the recommended dose based on area under the curve (AUC). No clinical data is available with tovorafenib in pregnancy in humans. The proposed label states to advise pregnant women and females of reproductive potential of the potential risk to a fetus. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting tovorafenib and to use effective non-hormonal contraception during treatment with tovorafenib and for 28 days after the last dose. In addition, in males with female partners of reproductive potential it is recommended to use effective non-hormonal contraception during treatment with tovorafenib and for 2 weeks after the last dose. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.6. NF1 Associated Tumors

Section 5.6 of the draft labeling states that tovorafenib may promote tumor growth in patients with NF1 tumors based on nonclinical data in NF1 models without BRAF alterations. The proposed label recommends to confirm evidence of a BRAF alteration prior to initiation of treatment with tovorafenib. If approved, this risk will be communicated in the warnings and precautions section of the label.

6. Expected Postmarket Use

If approved, tovorafenib will primarily be used in both inpatient and outpatient settings. The likely prescribers will be oncologists who specialize in this type of CNS tumor. Patient's caregivers will be involved in treatment including monitoring for adverse effects.

7. Risk Management Activities Proposed by the Applicant

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

8. Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of tovorafenib on the basis of the efficacy and safety information currently available. The indication will be approved under accelerated approval based on response rate and duration of response. Tovorafenib is a kinase inhibitor and will be the first targeted agent to be approved for the treatment of patients with pediatric LGG harboring BRAF fusions and rearrangements, including the KIAA1549:BRAF fusion. The efficacy of tovorafenib was supported by study FIREFLY-1 Arm 1, in which the tovorafenib group had an ORR of 51%**.** The serious risks associated with tovorafenib of hemorrhage, skin toxicity including photosensitivity, hepatotoxicity, effect on growth, embryo-fetal toxicity, and NF1 associated tumors will be communicated in the warnings and precautions section of the label.

Low grade gliomas are the most common cause of central nervous system tumors in children. The annual incidence of pediatric LGG in the United States is 1000 to 1600 cases. Most tumors harbor a single identifiable driver alteration, with BRAF alterations occurring in up to 70% of pediatric LGG. Patients with LGG rarely develop malignant transformation and the 10-year overall survival rate is greater than 90%. The likely prescribers will be oncologists who should have experience managing the serious adverse events reported with tovorafenib and other kinase inhibitors. The FDA clinical reviewer stated the while tovorafenib can cause significant toxicities, the toxicities are generally acceptable in the context of a serious disease and are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations in product labeling. If approved, based on the efficacy and risks associated with tovorafenib for patients 6 months of age and older with relapsed or refractory pediatric LGG harboring a BRAF fusion, rearrangement, or BRAF V600 mutation, the DRM and DO2 agree that a REMS is not necessary to ensure that the benefits outweigh the risks as the risk can be adequately communicated in labeling.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for tovorafenib 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 tovorafenib as currently edited by FDA, last accessed April 19, 2024.

[2] Tovorafenib NDA 217700 and NDA 218033 multi-disciplinary review and evaluation. Accessed April 14, 2024.

[3] de Blank P, Bandopadhayay P, Haas-Kogan D, Fouladi M, Fangusaro J. Management of pediatric low-grade glioma. *Curr Opin Pediatr*. 2019;31(1):21-27.

[4] Ryall S, Tabori U, Hawkins C. Pediatric low-grade glioma in the era of molecular diagnostics. *Acta Neuropathol Commun*. 2020;8(1):30.

[5] Bouffet E, Hansford JR, Garrè ML, et al. Dabrafenib plus Trametinib in Pediatric Glioma with BRAF V600 Mutations. *N Engl J Med*. 2023;389(12):1108-1120.

[6] Sievert AJ, Fisher MJ. Pediatric low-grade gliomas. *J Child Neurol*. 2009;24(11):1397-408.

[7] Tafinlar (dabrafenib) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2024 March.

[8] Mekinist (trametinib) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2024 March.

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/

BRAD T MORIYAMA
04/22/2024 11:48:57 PM

NAOMI S BOSTON
04/23/2024 09:11:05 AM

LAURA A ZENDEL
04/23/2024 11:04:11 AM