CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214200Orig1s000

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	214200
PDUFA Goal Date	February 15, 2021
OSE RCM #	2020-1258, 2020-1260
Reviewer Name(s)	Brad Moriyama, Pharm.D., BCCCP
Team Leader	Naomi Boston, Pharm.D.
Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	February 3, 2021
Subject	Evaluation of Need for a REMS
Established Name	trilaciclib
Trade Name	Cosela
Name of Applicant	G1 Therapeutics, Inc.
Therapeutic Class	kinase inhibitor
Formulation(s)	300 mg vial
Dosing Regimen	trilaciclib 240 mg/m^2 intravenous infusion completed within 4 hours of the start of chemotherapy on each day chemotherapy is administered

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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 Cosela (trilaciclib) is necessary to ensure the benefits outweigh its risks. G1 Therapeutics, Inc. submitted a New Drug Application (NDA) 214200 for trilaciclib with the proposed indication to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC). The serious risks associated with trilaciclib include injection-site reactions, including phlebitis and thrombophlebitis, acute drug hypersensitivity reactions, interstitial lung disease/pneumonitis, and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan.

The DRM and the Division of Non-Malignant Hematology (DNH) agree that a REMS is not necessary to ensure the benefits of trilaciclib outweigh its risks. The efficacy of trilaciclib was supported by Study G1T28-05, in which the trilaciclib group had a lower duration of severe neutropenia and a lower proportion of patients with severe neutropenia. The serious risks associated with trilaciclib of injection-site reactions, including phlebitis and thrombophlebitis, acute drug hypersensitivity reactions, interstitial lung disease/pneumonitis, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label. The likely prescribers will be hematologists and oncologists who should have experience managing the serious adverse events reported with trilaciclib.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Cosela (trilaciclib) is necessary to ensure the benefits outweigh its risks. G1 Therapeutics, Inc. submitted a NDA 214200 for trilaciclib with the proposed indication to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).[1] This application is under review in the Division of Non-Malignant Hematology (DNH). The applicant did not submit a proposed REMS or risk management plan.

2 Background

2.1 PRODUCT INFORMATION

Cosela (trilaciclib), a NME, is a kinase inhibitor, proposed to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for ES-SCLC. Trilaciclib is an inhibitor of cyclin-dependent kinase 4 and 6.[2] It is supplied as a 300 mg vial for IV injection. The proposed dosing regimen is trilaciclib 240 mg/m^2 intravenous infusion completed within 4 hours of the start of chemotherapy on each day chemotherapy is administered.[b] Trilaciclib was designated as breakthrough therapy. Trilaciclib is not currently approved in any jurisdiction.

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

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

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for trilaciclib NDA 214200 relevant to this review:

- 08/01/2019: Breakthrough therapy designation granted
- 06/15/2020: NDA 214200 submission to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for ES-SCLC received
- 10/09/2020: 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 trilaciclib

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

The estimated number of new cases of lung and bronchus cancer in the United States in 2021 is 235,760.[3] In addition, the estimated number of new cases of small cell lung cancer in the United States in 2019 was 29,660.[4,c] Approximately 60% to 70% of patients have ES-SCLC and 33% of patients have limited-stage small cell lung cancer at diagnosis.[5] Chemotherapy-induced myelosuppression, including neutropenia, anemia, and thrombocytopenia, may result in infection, sepsis, bleeding, and decreased health related quality of life.[2,6,d] Guidelines from the National Comprehensive Cancer Network (NCCN) for hematopoietic growth factors list topotecan as an example of a chemotherapy regimen in small cell lung cancer with a high risk for febrile neutropenia (> 20%).[7] Etoposide/carboplatin is listed as an example of a chemotherapy regimen in small cell lung cancer with an intermediate risk for febrile neutropenia (10% to 20%).

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Guidelines from the NCCN for hematopoietic growth factors recommend prophylactic use of granulocyte colony-stimulating factors (G-CSF) in patients receiving chemotherapy regimens with a high risk for febrile neutropenia (> 20%) and recommend individualized consideration of prophylactic G-CSF based on patient-specific risk factors in patients receiving chemotherapy regimens with an intermediate risk for febrile neutropenia (10% to 20%).[7]

Filgrastim and its biosimilars, which are leukocyte growth factors, were approved by the FDA to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever.[8] In addition, tbo-filgrastim, a leukocyte growth factor, was approved by the FDA in adult and pediatric patients 1 month and older for reduction in the duration of severe

[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.*

neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.[9] Furthermore, pegfilgrastim and its biosimilars, which are leukocyte growth factors, were approved by the FDA to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.[10] Filgrastim, filgrastim biosimilars, tbo-filgrastim, pegfilgrastim, and pegfilgrastim biosimilars do not have a boxed warning in their respective labels or have required a REMS for approval.

4 Benefit Assessment

The efficacy of trilaciclib to decrease the incidence of chemotherapy-induced myelosuppression was demonstrated in a Phase 2 study in patients receiving carboplatin, etoposide, and atezolizumab for newly diagnosed ES-SCLC (NCT 03041311, G1T28-05).[1,11,12] Supportive studies included a Phase 1b/2a study in patients receiving etoposide/carboplatin for newly diagnosed ES-SCLC (NCT 02499770, G1T28-02) and a Phase 1b/2a study in patients receiving topotecan for previously treated ES-SCLC (NCT 02514447, G1T28-03). The three studies were randomized, double-blind, and placebo controlled trials.

In Study G1T28-05, 107 patients were randomized to trilaciclib (N= 54) or placebo (N = 53) prior to administration of etoposide, carboplatin, and atezolizumab. The induction regimen was carboplatin (AUC 5) and atezolizumab 1200 mg on Day 1 and etoposide 100 mg/m^2 on Days 1, 2, and 3 of a 21-day cycle for a maximum of 4 cycles. Trilaciclib 240 mg/m^2 or placebo was administered on Days 1, 2, and 3 of a 21-day cycle for a maximum of 4 cycles. The maintenance regimen was atezolizumab 1200 mg on Day 1 of a 21-day cycle continued until disease progression or unacceptable toxicity. The primary efficacy endpoints were duration of severe neutropenia in Cycle 1 and occurrence of severe neutropenia. The mean duration of severe neutropenia in Cycle 1 was 0 days in the trilaciclib group and 4 days in the placebo group (mean difference -3.6, 95% CI -4.9 to -2.3, $p < 0.0001$). The occurrence of severe neutropenia was 1.9% in the trilaciclib group and 49.1% in the placebo group (adjusted relative risk 0.038, 95% CI 0.008 to 0.195, $p < 0.0001$).

In Study G1T28-02, 77 patients were randomized to trilaciclib (N= 39) or placebo (N = 38) prior to administration of etoposide and carboplatin. The dosing regimen for carboplatin/etoposide was carboplatin (AUC 5) on Day 1 and etoposide 100 mg/m^2 on Days 1, 2, and 3 of a 21-day cycle until disease progression or unacceptable toxicity. Trilaciclib 240 mg/m^2 or placebo was administered on Days 1, 2, and 3 of a 21-day cycle. The mean duration of severe neutropenia in Cycle 1 was 0 days in the trilaciclib group and 3 days in the placebo group. The number of patients with severe neutropenia was 5.1% in the trilaciclib group and 42.1% in the placebo group.

In Study G1T28-03, 61 patients were randomized to trilaciclib (N= 32) or placebo (N = 29) prior to administration of topotecan. The dosing regimen for topotecan was 1.5 mg/m^2 on Days 1 to 5 of a 21-day cycle until disease progression or unacceptable toxicity. Trilaciclib 240 mg/m^2 or placebo was administered on Days 1 to 5 of a 21-day cycle. The mean duration of severe neutropenia in Cycle 1 was 2 days in the trilaciclib group and 7 days in the placebo group. The number of patients with severe neutropenia was 40.6% in the trilaciclib group and 75.9% in the placebo group.

The FDA clinical reviewer concluded in Study G1T28-05, the trilaciclib group had a lower duration of severe neutropenia and a lower proportion of patients with severe neutropenia.[11,e] However, they concluded in studies G1T28-02 and G1T28-03 the efficacy examination was exploratory.[12]

5 Risk Assessment & Safe-Use Conditions

The safety of trilaciclib was evaluated in a Phase 2 clinical trial in patients receiving carboplatin, etoposide, and atezolizumab for newly diagnosed ES-SCLC (NCT 03041311, G1T28-05), in a Phase 1b/2a clinical trial in patients receiving etoposide/carboplatin for newly diagnosed ES-SCLC (NCT 02499770, G1T28-02), and in a Phase 1b/2a clinical trial in patients receiving topotecan for previously treated ES-SCLC (NCT 02514447, G1T28-03).[1,11,f] In the combined safety population from G1T28-05, G1T28-02, and G1T28-03, 122 patients received trilaciclib and 118 patients received placebo. Common adverse reactions reported with trilaciclib included fatigue, hypocalcemia, hypokalemia, hypophosphatemia, increased aspartate aminotransferase, (b) (4), and headache.

The serious risks[g] associated with trilaciclib which include injection-site reactions, including phlebitis and thrombophlebitis, acute drug hypersensitivity reactions, interstitial lung disease/pneumonitis, and embryo-fetal toxicity are summarized in the sections below.

5.1 Injection-Site Reactions, Including Phlebitis and Thrombophlebitis

An adverse event of injection-site reactions including phlebitis and thrombophlebitis occurred in 56/272 (21%) of patients receiving trilaciclib in clinical trials, with Grade 2 injection-site reactions including phlebitis and thrombophlebitis reported in 10% of patients and Grade 3 injection-site reactions including phlebitis and thrombophlebitis reported in 0.4% of patients. The proposed label recommends monitoring for signs and symptoms of injection site reactions, phlebitis, and thrombophlebitis, including infusion site pain and erythema during infusion. It recommends stopping the trilaciclib infusion and to permanently discontinue trilaciclib for Grade 3 or Grade 4 injection site reactions. If approved, this risk will be communicated in the warnings and precautions section of the label.

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[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.*

[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.

5.2 ACUTE DRUG HYPERSENSITIVITY REACTIONS

An adverse event of acute drug hypersensitivity reactions occurred in 16/272 (6%) of patients receiving trilaciclib in clinical trials, with Grade 2 acute drug hypersensitivity reactions reported in 2% of patients. The proposed label recommends monitoring for signs and symptoms of acute drug hypersensitivity reactions including facial, eye, and tongue edema, urticaria, pruritus, and anaphylactic reactions. It recommends stopping the trilaciclib infusion and to permanently discontinue trilaciclib for Grade 3 or Grade 4 acute drug hypersensitivity reactions. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.3 INTERSTITIAL LUNG DISEASE/PNEUMONITIS

Severe, life-threatening, or fatal interstitial lung disease and/or pneumonitis has been reported with cyclin-dependent kinase 4/6 inhibitors. An adverse event of interstitial lung disease/pneumonitis (Grade 3) occurred in 1/272 (0.4%) of patients receiving trilaciclib in clinical trials. The proposed label recommends monitoring for pulmonary symptoms of interstitial lung disease/pneumonitis. It recommends to permanently discontinue trilaciclib for recurrent Grade 2, Grade 3, or Grade 4 interstitial lung disease/pneumonitis. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.4 EMBRYO-FETAL TOXICITY

Trilaciclib may cause fetal harm based on the mechanism of action of the drug. No clinical data is available with trilaciclib in pregnancy in humans. The proposed label states to advise patients of the need for effective contraception. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting trilaciclib and that effective contraception be used during treatment and for at least 3 weeks after the final dose. If approved, this risk will be communicated in the warnings and precautions section of the label.

6 Expected Postmarket Use

If approved, trilaciclib will primarily be used in both inpatient and outpatient (such as infusion centers) settings. The likely prescribers will be oncologists and hematologists.

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

The FDA clinical reviewer recommends approval of trilaciclib on the basis of the efficacy and safety information currently available. Trilaciclib is a kinase inhibitor and may be a treatment option to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for ES-

SCLC. The efficacy of trilaciclib was supported by Study G1T28-05, in which the trilaciclib group had a lower duration of severe neutropenia and a lower proportion of patients with severe neutropenia. The serious risks associated with trilaciclib of injection-site reactions, including phlebitis and thrombophlebitis, acute drug hypersensitivity reactions, interstitial lung disease/pneumonitis, and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label.

The estimated number of new cases of small cell lung cancer in the United States in 2019 was 29,660. Approximately 60% to 70% of patients have ES-SCLC and 33% of patients have limited-stage small cell lung cancer at diagnosis. Chemotherapy-induced myelosuppression may be a cause of morbidity and mortality in patients. The likely prescribers will be hematologists and oncologists who should have experience managing the serious adverse events reported with trilaciclib. Based on the efficacy and risk associated with trilaciclib to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for ES-SCLC, the DRM and DNH recommendation is that a REMS is not necessary to ensure that the benefits outweigh the risks.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for trilaciclib 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 trilaciclib as currently edited by FDA, accessed February 2, 2021.

[2] G1 Therapeutics, Inc. Trilaciclib. Module 2.5. clinical overview. June 15, 2020.

[3] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33.

[4] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Small Cell Lung Cancer (version 2.2021 – January 11, 2021). https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf (accessed 2021 January 12).

[5] Wang S, Zimmermann S, Parikh K, Mansfield AS, Adjei AA. Current Diagnosis and Management of Small-Cell Lung Cancer. Mayo Clin Proc. 2019;94(8):1599-1622.

[6] Daniel D, Kuchava V, Bondarenko I, et al. Trilaciclib prior to chemotherapy and atezolizumab in patients

with newly diagnosed extensive-stage small cell lung cancer: A multicentre, randomised, double-blind, placebo-controlled Phase II trial. Int J Cancer. 2020. Epub ahead of print.

[7] National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Hematopoietic Growth Factors (version 2.2020 – January 27, 2020). https://www.nccn.org/professionals/physician_gls/pdf/growthfactors.pdf. (accessed 2021 January 12).

[8] Neupogen (filgrastim) package insert. Thousand Oaks, CA: Amgen Inc.; 2021 January.

[9] Granix (tbo-filgrastim) package insert. North Wales, PA: Teva Pharmaceuticals USA, Inc.; 2019 March.

[10] Neulasta (pegfilgrastim) package insert. Thousand Oaks, CA: Amgen Inc.; 2021 January.

[11] Dmytrijuk A, Robie-Suh K, Dwyer KL, Chen Y. Division of Non-Malignant Hematology (DNH). Trilaciclib. Mid-Cycle Meeting, clinical and statistics reviewer slides. September 18, 2020.

[12] Division of Biometrics IX Statistical Review and Evaluation Memorandum for NDA 214200. January 8, 2021.

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