CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211192Orig1s000

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	211192
PDUFA Goal Date	August 21, 2018
OSE RCM #	2017-2612; 2017-2614
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	June 6, 2018
Subject	Review to determine if a REMS is necessary
Established Name	Ivosidenib
Trade Name	Tibsovo
Name of Applicant	Agios Pharmaceuticals, Inc.
Therapeutic Class	Isocitrate dehydrogenase-1 inhibitor
Formulation(s)	250 mg tablet
Dosing Regimen	500 mg orally once daily until disease progression or unacceptable toxicity.

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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 ivosidenib (Tibsovo) is necessary to ensure the benefits outweigh its risks. Agios Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 211192 for ivosidenib with the proposed indication for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test. The serious risks associated with the use of ivosidenib are differentiation syndrome, QTc interval prolongation, Guillain-Barré syndrome, and embryo-fetal toxicity. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes a Boxed Warning, Warnings and Precautions, and a Medication Guide as part of labeling to inform patients regarding the serious risk of differentiation syndrome.

DRISK and the Division of Hematology Products (DHP) have determined that if approved, a REMS is not necessary to ensure the benefits of ivosidenib outweigh its risks. The current standard treatment for AML is intensive chemotherapy and an allogeneic stem cell transplant, which is based mainly on the patient's ability to tolerate the intensive regimen. There are no FDA-approved drugs that are specifically targeted treatments for IDH1 mutation-positive R/R AML, and there is no standard of care treatment regimen for these patients. Therefore, there remains a clear medical need for new treatments for patients with relapsed or refractory AML. In the clinical trial, ivosidenib appeared efficacious in both its primary and secondary outcomes. The most concerning adverse reaction associated with the use of ivosidenib is differentiation syndrome (DS). Similar to another IDH inhibitor, enasidenib, labeling will include the risk of DS as a Boxed Warning, and recommendations for its management, will be communicated in the Warnings and Precautions section of the product label.

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 ivosidenib (Tibsovo) is necessary to ensure the benefits outweigh its risks. Agios Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 211192 for ivosidenib with the proposed indication for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.[1] The applicant did not submit a REMS with this application but proposed Prescribing Information that includes a Boxed Warning, Warnings and Precautions, and a Medication Guide as part of labeling to inform patients regarding the serious risk of differentiation syndrome.

2 Background

2.1 PRODUCT INFORMATION

Ivosidenib is a NME NDA type 505(b)(1) pathway application.[a] It is an IDH1 inhibitor proposed for indication as treatment of adult patients with relapsed or refractory AML with an IDH1 mutation as detected by an FDA-approved test. Isocitrate dehydrogenases (IDH) catalyze the oxidative

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

decarboxylation of isocitrate to α-ketoglutarate (α-KG) during cellular metabolism. Mutations of the IDH1 isoform are found in 6-16% of patients with AML.[2] These mutations are typically heterozygous and confer a new ability of the enzyme to catalyze the production of 2-hydroxyglutarate (2-HG). Increased cellular 2-HG levels contribute to epigenetic mechanisms of pathogenesis by inhibiting α-KG-dependent enzymes important for normal DNA methylation. Ivosidenib was shown to inhibit a variety of IDH1 R132 mutants at much lower concentrations than wild-type IDH1 in vitro. Inhibition of the mutant IDH1 enzyme by ivosidenib led to decreased 2-hydroxyglutarate (2-HG) levels and induced myeloid differentiation in vitro and in vivo in mouse xenograft models of IDH1-mutated AML. Ivosidenib is prepared as 250 mg tablets to be taken by the oral route.[1,3] The recommended dose of ivosidenib is 500 mg taken orally once daily with or without food until disease progression or unacceptable toxicity.[b] Ivosidenib was granted fast track designation on May 13, 2015, and orphan drug designation on June 9, 2015. Ivosidenib is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for ivosidenib (NDA 211192) relevant to this review:

- 12/20/2013: Investigation New Drug (IND) 119341 submission was received.
- 05/13/2015: Fast track designation granted.
- 06/09/2015: Orphan Drug designation granted.
- 09/20/2017: Applicant informed at pre-NDA meeting that the need for a REMS for ivosidenib will be made upon reviewing the NDA.
- 12/21/2017: NDA 211192 submission for ivosidenib with the proposed indication for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test, received.
- 04/12/2018: 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 ivosidenib.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Acute myelogenous leukemia (AML) is a form of cancer that is characterized by infiltration of the bone marrow, blood, and other tissues by proliferative, clonal, abnormally differentiated, and occasionally poorly differentiated cells of the hematopoietic system.[4] The pathophysiology in AML consists of a maturational arrest of bone marrow cells in the earliest stages of development. The mechanism of this arrest is under study, but in many cases, it involves the activation of abnormal genes through chromosomal translocations and other genetic abnormalities. This developmental arrest results in 2 disease processes. First, the production of normal blood cells markedly decreases, which results in varying degrees of anemia, thrombocytopenia, and neutropenia. Second, the rapid proliferation of these cells, along with a reduction in their ability to undergo programmed cell death, results in their

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

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