CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209606Orig1s000

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	209606
PDUFA Goal Date	August 30, 2017
OSE RCM #	2017-16; 2017-18
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Acting Team Leader	Elizabeth Everhart, MSN, RN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	June 27, 2017
Subject	Review to determine if a REMS is necessary
Established Name	Enasidenib
Trade Name	Idhifa
Name of Applicant	Celgene
Therapeutic Class	Isocitrate dehydrogenase-2 inhibitor
Formulation(s)	50 mg and 100 mg tablets
Dosing Regimen	100 mg 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 enasidenib (Idhifa) is necessary to ensure the benefits outweigh its risks. Celgene submitted a New Drug Application Application (NDA) 209606 for enasidenib with the proposed indication as treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Boxed Warning, Warnings and Precautions and a Medication Guide as part of labeling to inform patients regarding the potential risks of differentiation syndrome.

DRISK and Division of Hematology Products (DHP) have determined that if approved, a REMS is not necessary to ensure the benefits of enasidenib outweigh its risks. The current standard treatment for AML is intensive chemotherapy potentially leading to an allogeneic stem cell transplant and is based mainly on the patient's ability to tolerate intensive treatment. There are no FDA-approved drugs specifically for relapsed or refractory AML, and there is no standard of care treatment regimen for these patients. Therefore, there remains a clear medical need for new treatments for these patients. In the clinical trial, enasidenib appeared efficacious in both its primary and secondary outcomes. The most concerning adverse reaction associated with the use of enasidenib is differentiation syndrome; this risk, and recommendations for its management, will be communicated in the Boxed Warning and 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 (NME) enasidenib (Idhifa) is necessary to ensure its benefits outweigh its risks. Celgene submitted a New Drug Application Application (NDA) 209606 for enasidenib with the proposed indication as treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation.[1] This application is under review in the Division of Hematology Products (DHP). The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Boxed Warning, Warnings and Precautions and a Medication Guide as part of labeling to inform patients regarding the potential risks of differentiation syndrome.

2 Background

2.1 PRODUCT INFORMATION

Enasidenib is a NME NDA type 505(b)(1) pathway application.[a] It is an IDH2 inhibitor proposed for indication as treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation. Enasidenib inhibits certain mutant forms of IDH2 including R140Q, R172K, and R172S at approximately 40-fold lower concentrations than wild-type IDH2. The IDH enzymes catalyze the oxidative decarboxylation of isocitrate to alpha-ketoglutarate (α-KG), producing nicotinamide adenine dinucleotide phosphate (NADPH) in the process via the citric acid cycle. Enasidenib is prepared as 50 mg

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

and 100 mg tablets to be taken by the oral route.[1,2] The proposed starting dose of enasidenib is 100 mg taken orally once daily until disease progression or unacceptable toxicity.[b] Enasidenib was granted an Orphan drug designation on June 12, 2014, and a fast track designation on July 31, 2014. Enasidenib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for enasidenib (NDA 209606) relevant to this review:

- 07/18/2013: Investigation New Drug (IND) 117631 submission was received.
- 06/12/2014: Orphan Drug designation granted.
- 07/31/2014: Fast track designation granted.
- 07/26/2016: Applicant informed at pre-NDA meeting that FDA has preliminary concerns about the risk of differentiation syndrome and appropriate management guidelines may need to be communicated effectively to physicians in some manner. The need for a REMS for enasidenib will be made upon reviewing the NDA.
- 12/30/2016: NDA 209606 submission for enasidenib with the proposed indication for the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation, received.
- 04/28/2017: 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 enasidenib.

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.[3] 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 accumulation in the bone marrow, the blood, the spleen, and the liver.[4] The American Cancer Society estimates that approximately about 21,380 new cases of AML will be diagnosed in United States[c], and

[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.*

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