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.*

accumulation in the bone marrow, the blood, the spleen, and the liver.[5,8] The American Cancer Society estimates that approximately 19,520 new cases of AML, mostly in adults, will be diagnosed in United States[c], and there will be about 10,670 deaths from AML in 2018 with almost all in adults.[d] Acute myeloid leukemia is generally a disease of older people and is uncommon before the age of 45. The average age of a patient with AML is 67 years.[6]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The general therapeutic strategy in patients with AML has not changed substantially in more than 30 years. The standard treatment is intensive chemotherapy and an allogeneic stem cell transplant, which is based mainly on the patient's ability to tolerate intensive treatment. Treatment of AML has been divided into induction chemotherapy and postremission (e.g. consolidation) therapy.[4] Although obtaining a remission is the first step in controlling the disease, it is also important for patients to emerge from the induction phase in a condition to tolerate subsequent more intensive treatments during consolidation to achieve durable disease control. Patients who do not receive postremission therapy may experience relapse, usually within 6 to 9 months.[7] A complete response is achieved in 60 to 85% of adults who are 60 years of age or younger. In patients who are older than 60 years of age, complete response rates are inferior (40 to 60%).[4] Although advances in the treatment of AML have led to significant improvements in outcomes for younger patients, prognosis in the elderly, who account for the majority of new cases, remains poor.[8] Therefore, treatment results are generally analyzed separately for younger (18-60 years) patients and for older patients (>60 years). In patients who can tolerate intensive therapy, which may be limited by factors such as age and comorbid conditions, cytarabine and daunorubicin induction followed by high-dose cytarabine consolidation is frequently used. Intensifying induction therapy with a high daily dose of anthracycline plus intensive consolidation therapy resulted in a high complete-remission rate and prolonged overall survival in patients with AML. This regimen typically results in CR rates of 60-70% and 2-year OS of approximately 50% in patients < 60 years of age.[9] Older patients fare less well, with CR rates of approximately 50% and 2-year overall survival of approximately 20%.[10]

Patients who are fit for intensive therapy should receive a salvage chemotherapy regimen followed by HSCT. About half will achieve a second complete remission, and 5-year survival of patients who achieve a second remission is about 40%.[11] In large, phase 3 studies of high-dose cytarabine or investigator's choice (e.g., hypomethylating agents, multi-agent chemotherapy, cytarabine, hydroxyurea, or supportive care) in primary refractory AML or AML that has relapsed after 1 or more prior regimens, the rate of CR ranges from 12 to 16%, and median OS ranges from 3.3 to 6.3 months. In 2017 the following therapies were approved for AML: enasidenib (Idhifa) for the treatment of IDH2-mutated relapsed or refractory (R/R) AML[12], midostaurin (Rydapt) for the treatment of patients with newly diagnosed AML with FLT3 mutations[13]; daunorubicin and cytarabine (Vyxeos) for the treatment of newly diagnosed therapy-related AML or AML with myelodysplasia-related changes[14]; and gemtuzumab ozogamicin (Mylotarg) for the treatment of adults with newly diagnosed CD33-positive AML, and for the treatment of patients aged ≥2 years with CD33-positive AML who have experienced a relapse or who have not

[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.*

responded to initial treatment (refractory)[15]. Despite the availability of new therapies, the long-term prognosis for patients with R/R AML remains limited and there are no FDA-approved drugs that are specifically targeted treatments for IDH1 mutation-positive R/R AML. There is a clear need for new treatments for patients with relapsed or refractory AML.[16]

4 Benefit Assessment

The efficacy of ivosidenib was evaluated in an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839). The study population included 173 adult patients with relapsed or refractory AML who were assigned to receive a 500 mg of ivosidenib daily and who had IDH1 mutations identified by the Abbott RealTime IDH1 assay, which is the FDA-approved test for selection of patients with AML for treatment with ivosidenib.

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for ivosidenib. Efficacy was established on the basis of the rate of complete remission (CR) plus complete remission with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. (b) (4) The median follow-up was (b) (4) (range, 0.2 to 39.5 months) and median treatment duration was 4.1 months (range, 0.1 to 39.5 months).

Table 1: Efficacy Results in Patients with Relapsed or Refractory AML[1,16]

Endpoint	**Ivosidenib (500 mg daily) N=** (b) (4)
CR[1] n (%)	43 (b) (4)
95% CI	(b) (4)
Median DOR[2] (months)	10.1
95% CI	(6.5, 22.2)
CRh[3] n (%)	14 (b) (4)
95% CI	(4.5, (b) (4)
Median DOR (months)	3.60
95% CI	(1, 5.5)
CR+CRh[4] n (%)	57 (b) (4)
95% CI	(b) (4)
Median DOR (months)	8.2
95% CI	(5.6, 12)

CI: confidence interval

[1] CR (complete remission) was defined as <5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter).

[2] DOR (duration of response) was defined as time since first response of CR or CRh to relapse or death, whichever is earlier.

[3] CRh (complete remission with partial hematological recovery) was defined as <5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

[4] CR+CRh rate appeared to be consistent across all baseline demographic and baseline disease characteristics with the exception of number of prior regimens.

The secondary efficacy endpoints included CR rate, overall response rate (ORR), duration of CR+CRh, duration of CR (DOCR), duration of response (DOR), overall survival (OS), event-free survival (EFS), time to CR+CRh, time to CR, time to response, and transfusion independence. The clinical reviewer stated as the OS is not interpretable in single arm studies and EFS did not consider treatment failures, the duration of CR+CRh and DOCR should be more helpful to assess the length of meaningful responses in the patient population. An observed CR+CRh rate in R/R AML subjects with the lower bound of the exact binomial 95% CI greater than 10% was deemed as clinically meaningful. This was considered to be evidence of clinically significant activity from ivosidenib.[16,17, e]

For patients who achieved a CR or CRh, the median time (b) (4) to CR or CRh was 2 months (range, 0.9 to 5.6 months). Of the 57 patients who achieved a best response of CR or CRh, all achieved a first response of CR or CRh within 6 months of initiating ivosidenib. Among the (b) (4) patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 41 (b) (4) %) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 64 patients who were independent of both RBC and platelet transfusions at baseline, 38 (59.4%) remained transfusion independent during any 56-day post-baseline period.[1]

5 Risk Assessment & Safe-Use Conditions

At the time of this writing, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant safety information to date for ivosidenib. The safety analysis of ivosidenib primarily focuses on 179 adult patients with relapsed or refractory AML treated with 500 mg daily (R/R AML SAS). The median duration of exposure to ivosidenib was 3.9 months (range 0.1 to 39.5 months). Sixty-five patients (36%) were exposed to ivosidenib for at least 6 months and 16 patients (9%) were exposed for at least 1 year.

The most common adverse reactions (≥20%) of any grade were fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, electrocardiogram QT prolonged, rash, pyrexia, and constipation.

Deaths

There were a total of 129 (72%) all deaths and 50 on-treatment deaths (28% on or within 28 days after the last dose of ivosidenib) in the R/R AML SAS of 179 patient pool. The FDA determined that the majority (n=40, 80%) of the on-treatment deaths in R/R AML patients on Study AG120-C-001 were due to the primary malignancy. There were 10 deaths (5.6%) in R/R AML patients on AG120-C-001 considered by the FDA to be at least possibly related to ivosidenib. Infection was clearly the cause of death in 3 cases. There were 7 deaths in R/R AML patients not definitively caused by infection that were considered by the FDA to be a direct toxicity of ivosidenib, in which 3 of the cases include manifestations of DS, although all the cases have other possible causes of death (e.g. infection, underlying malignancy). (See Section on differentiation on syndrome).[16] Due to the overlap in clinical manifestations, it is difficult to distinguish between differentiation syndrome and infection. It is also difficult to determine conclusively whether DS contributed to progression of a pre-existing or developing infection. Four of the

[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.*

cases have other possible causes of death (e.g. aspiration pneumonia, pericarditis/myocarditis, ventricular arrhythmia, Thrombotic stroke). FDA could not rule out the possibility that ivosidenib contributed to these deaths.[16] The all-cause mortality as calculated by the FDA for the 179 subjects in the R/R AML SAS was 7% (95% CI, 4-11%) at day 30, 15% (95% CI 10-20%) at day 60, and 20% (95% CI, 15-27%) at day 90.[16] The clinical reviewers stated that the all-cause mortality observed in patients treated with ivosidenib compares favorably to the 10-20% seen in patients treated with chemotherapy.[16]

Serious Adverse Events (SAE)

Serious adverse reactions (≥ 5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). The most common adverse reactions leading to dose interruption were electrocardiogram QT prolonged (7%), differentiation syndrome (3%), leukocytosis (3%) and dyspnea (3%). Three out of 179 patients (2%) required a dose reduction due to an adverse reaction. Adverse reactions leading to a dose reduction included electrocardiogram QT prolonged (1%), diarrhea (1%) nausea (1%) decreased hemoglobin (1%) and increased transaminases (1%). Adverse reactions leading to permanent discontinuation included Guillain-Barre syndrome (1%) and rash (1%), and increased creatinine (1%).

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 DIFFERENTIATION SYNDROME:

In the clinical trial, (b) (4)% ((b) (4)/179) patients with relapsed or refractory AML treated with ivosidenib experienced differentiation syndrome (b) (4). Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with ivosidenib included noninfectious leukocytosis (b) (4), peripheral edema (b) (4), pyrexia (b) (4), dyspnea (b) (4), pleural effusion (b) (4), hypotension (b) (4), hypoxia (b) (4), pulmonary edema (b) (4) pneumonia (b) (4), pericardial effusion (b) (4), rash (b) (4) fluid overload (b) (4) tumor lysis syndrome (b) (4) and (b) (4) Of the (b) (4) patients who experienced differentiation syndrome, (b) (4) recovered after treatment or after dose interruption of ivosidenib. Differentiation syndrome occurred as early as (b) (4) days and up to (b) (4) months after ivosidenib initiation and has been observed with or without concomitant leukocytosis.[1]

The 3 deaths showed manifestations of DS, although all the cases have other possible causes of death (e.g. infection, underlying malignancy). Death occurred in one patient, who was diagnosed with Aspergillosis and voriconazole was started. Five days after the final dose of ivosidenib, the patient died due to ARDS, assessed as due to the underlying malignancy. FDA assessed the cause of death to be due to the underlying malignancy and believes that DS may have contributed. The second patient was thought to have died from respiratory failure as a consequence of his AML. His WBC increased substantially around the time of his respiratory decompensation, renal failure, and hypotension. However, his peripheral blast count decreased steadily from a peak of 75% on day 18 to only 10% on day 45, arguing somewhat against progression of disease. Infection is another possibility, but cultures were all negative. In the absence of a definitive alternative, DS as the cause of death could not be ruled out. The third patient was diagnosed with febrile bilateral pneumonia with chronic neutropenia and was treated with antibiotics. The final dose of study treatment was day 15 and 1 day later the patient died of sepsis including pulmonary infection, assessed as due to the underlying malignancy. Although the patient had a high burden of leukemia and possible pulmonary sepsis, no organism was identified. FDA

could not rule out that the pre-existing process in the lungs may have been exacerbated by DS (concomitant fever, polypnea, pleuropericardial effusions, and peripheral edema). (See clinical review for a detailed patient narratives).[16]

Similar to another IDH inhibitor, enasidenib, labeling will include the risk of DS as a Boxed Warning. Management of DS, including recommendations for initiating oral or intravenous steroids and hemodynamic monitoring, will likely also be communicated in the Warnings and Precautions section of the label to increase the prominence of this information and promote mitigation of DS; a Medication Guide as part of labeling to inform patients regarding the potential risks of DS will also be included. Monitoring and dosage modifications for toxicities to address the safety issues with ivosidenib will likely be included in the Dosage and Administration section of the label.

5.2 QTc Interval Prolongation:

QT (QTc) interval prolongation can develop in patients treated with ivosidenib. Of the 258 patients treated with ivosidenib in the clinical trial, 9% (n=17) were found to have a QTc interval greater than 500 msec (Grade ≥3) and 14% (n=22) of patients had an increase from baseline QTc greater than 60 msec. Three patients (1%) developed ventricular arrhythmia, including ventricular fibrillation and ventricular tachycardia. Among the 179 subjects with R/R AML whose starting dose was 500 mg QD, results from the categorical analysis of the maximum post-baseline increase in QTcF from baseline showed that in the majority of subjects who had an increase in post-baseline QTcF, the increase was ≤60 msec. The change from baseline (ΔQTcF) reported in clinical trial for ≤ 30msec, >30 to ≤60 msec, and >60 msec were 45.3% (n=81), 42.5% (n=76), and 12.3% (n=22), respectively.[18] The clinical trial excluded patients with baseline QTc of ≥450 msec (unless the QTc ≥ 450 msec was due to a pre-existing bundle branch block) or with a history of long QT syndrome or uncontrolled or significant cardiovascular disease.[1] Grade ≥3 AEs of electrocardiogram QT prolonged occurred in 18 subjects (10.1%); Grade ≥3 AEs were assessed as treatment-related in 14 subjects (7.8%). There were no Grade 4 AEs of electrocardiogram QT prolonged and no AEs with a fatal outcome. The incidence of dose reductions due to AEs of electrocardiogram QT prolonged was low (2 subjects, 1.1%); dose holds were reported in 13 subjects (7.3%). There were no AEs of electrocardiogram QT prolongation that led to study treatment discontinuation. Serious adverse events were reported in 12 subjects (6.7%); none of the SAEs were fatal. There were no reported cases of Torsade de Pointes or Sudden Death. The risk of QTc interval prolongation as well as monitoring will likely be communicated in the Warnings and Precautions section of the label. Monitoring and dosage modifications for toxicities to address the safety issues with ivosidenib will likely be included in the Dosage and Administration section of the label.

5.3 Guillain-Barré Syndrome:

Guillain-Barré syndrome occurred in <1% (2/258) of patients treated with ivosidenib in the clinical study.[1] The proposed label includes recommendation for the monitoring patients for onset of new signs symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, or parasthesias. The risk of Guillain-Barré syndrome as well as monitoring for it will likely be communicated in the Warnings and Precautions and Dosage and Administration sections of the label.

(b) (4)

(b) (4)

Other Serious Adverse Events (SAE)

Leukocytosis

A total of 65 (36.3%) of subjects with R/R AML whose starting dose was 500 mg QD experienced leukocytosis events. Grade ≥3 events were reported in 15 subjects (8.4%); most were assessed as unrelated to study treatment. These events were reported as SAEs in 18 subjects (10.1%); none were fatal. The risk of leukocytosis will likely be communicated in the Adverse Reactions section of the label. Management of leukocytosis, including recommendations for initiating hydroxyurea and hemodynamic monitoring, will likely be communicated in the Dosage and Administration section of the label to promote mitigation of leukocytosis.

Tumor Lysis Syndrome

A total of 12 (6.7%) of subjects with R/R AML whose starting dose was 500 mg QD had at least 1 AE of tumor lysis syndrome (TLS); none of the events were assessed by the Investigator as treatment-related. Grade ≥3 events of TLS were reported in 10 subjects (5.6%). TLS was reported as an SAE in 6 subjects (3.4%); none of the SAEs resulted in a fatal outcome. No subjects discontinued study treatment or required a dose reduction for management of this event; study treatment was held in 1 subject (0.6%). The risk of TLS will be communicated will likely be communicated in the Adverse Events section of the label.

6 Expected Postmarket Use

The proposed indication is for the treatment of adult patients with relapsed or refractory AML with an IDH1 mutation. It is expected that oncologists/hematologists, who are familiar with the management of chemotherapeutic toxicities such as DS, embryo-fetal toxicity, leukocytosis and tumor lysis syndrome, will be the likely health care providers to prescribe ivosidenib in both inpatient and outpatient setting.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for ivosidenib beyond routine pharmacovigilance and labeling. The applicant proposed a Boxed Warning in the labeling and a Medication Guide as part of labeling to inform patients regarding the potential risks of differentiation syndrome.

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for ivosidenib, DRISK considers patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Ivosidenib is an IDH1 inhibitor proposed for indication as treatment of adult patients with relapsed or refractory AML with an IDH1 mutation. Based on the efficacy and safety information currently available, the clinical reviewers stated that ivosidenib shows clinical meaningful benefit to patients with AML, and recommends approval of ivosidenib for the treatment of adult patients with relapsed or refractory AML with an IDH1 mutation.[16]

DRISK and DHP have determined that if approved, a REMS is not necessary to ensure the benefits of ivosidenib outweigh its risks. Labeling, including a Boxed Warning, and Warnings and Precautions will be used to communicate the safety issues and management of toxicities associated with ivosidenib. The most concerning adverse reactions observed with the use of ivosidenib are DS, QTc interval prolongation, Guillain-Barré syndrome, and embryo-fetal toxicity. Ivosidenib appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling. The current standard treatment for AML is intensive chemotherapy and an allogeneic stem cell transplant; treatment 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 the patients with relapsed or refractory AML.

Similar to another IDH inhibitor, enasidenib, labeling will include the risk of DS as a Boxed Warning; recommendations for the management of DS will be included in the Warnings and Precautions section of the label to increase the prominence of this information and promote its mitigation; a Medication Guide as part of labeling to inform patients regarding the potential risks of differentiation syndrome will also be included.

There are other oncology products that prolong the QT interval. Caprelsa (vandetinib) was approved with a REMS that included elements to assure safe use to address the risk of QT prolongation, Torsades de pointes, and sudden death. Based on the exposure-response relationship, the mean (90% CI) QTcF change from baseline (ΔQTcF) was 35 ms for Caprelsa. In addition, 36% of patients experienced greater than 60 ms increase in ΔQTcF and 4.3% of patients had QTcF greater than 500 ms. There were 11 cases of sudden death and 2 documented cases of Torsades de pointes (TdP) in Caprelsa's clinical studies.[19]

Tasigna (nilotinib) was initially approved with MG and CP in March 2010. The maximum mean QTcF change from baseline at steady-state was 10 msec. Increase in QTcF greater than 60 msec from baseline was observed in 4.1% of the patients and QTcF of greater than 500 msec was observed in 4 patients (less than 1%). Ten cases of sudden deaths were reported in the original nilotinib NDA.[20] REMS assessments for Tasigna indicated that a high percentage of the prescriber population was aware of ECG monitoring intended to identify patients at risk and enhance early detection and treatment of QT prolongation; the REMS is released in May 2013.[21]The approved product label of Caprelsa contains a Boxed Warning for QT Prolongation, Torsades De Pointes and Sudden Death whereas Tasigna contain a Boxed Warning for QT Prolongation and Sudden Death.[22,23]

Of the 179 patients treated with ivosidenib in the clinical trial, 10% were found to have a QTc greater than 500 msec (Grade ≥3) and 13% of patients had an increase from baseline QTc greater than 60 msec. There were no reported cases of Torsade de Pointes or Sudden Death with ivosidenib related to QTc interval prolongation. The risks of QTc interval prolongation, Guillain-Barré syndrome, and embryo-fetal toxicity will likely be communicated in the Warnings and Precautions section of the label. The adverse reactions of leukocytosis and TLS will likely be communicated in the Adverse Reactions section of the label. Monitoring and dosage modifications for toxicities to address the safety issues with ivosidenib will likely be included in the Dosage and Administration section of the label. Additionally, the applicant will be required to conduct a post-marketing required (PMR) study to characterize the long-term safety of ivosidenib in patients with relapsed or refractory acute myeloid leukemia (AML).[24]

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh the risks of ivosidenib. The management of the risks associated with ivosidenib treatment can be communicated through labeling. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated specifically REMS.

10 References

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/s/

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06/06/2018

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