CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207997Orig1s000
207997Orig2s000

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	207997
PDUFA Goal Date	April 28 ,2017
OSE RCM #	2016-1924, 2016-2080
Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader	Naomi Redd, Pharm.D.
Division Director	Cynthia Lacivita, Pharm.D.
Review Completion Date	February 13, 2017
Subject	Evaluation of Need for a REMS
Established Name	Midostaurin
Trade Name	Rydapt
Name of Applicant	Novartis
Therapeutic Class	Kinase Inhibitor
Formulation(s)	25 mg capsule
Dosing Regimen	50 mg oral twice daily for acute myeloid leukemia (AML) on days 8 to 21 of each cycle of induction with daunorubicin and cytarabine and on days 8 to 21 of each cycle of consolidation with high-dose cytarabine. 100 mg oral twice daily for aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

Table of Contents

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 (NME) Rydapt (midostaurin) is necessary to ensure the benefits outweigh its risks. Novartis submitted a New Drug Application (NDA) 207997 for midostaurin with two indications. The first indication is for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FMS-like tyrosine kinase 3 (FLT3) mutation positive as detected by an FDA-approved test Midostaurin is to be used in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation, it is not indicated as a single agent therapy for patients with AML. The second indication is for the treatment of aggressive systemic mastocytosis (ASM), systemic matocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

The serious risks associated with midostaurin include pulmonary toxicity and nonclinical findings of embryo-fetal abnormalities and embryo-fetal death. The risk of embryo-fetal toxicity will be included in the label as a Boxed Warning, while pulmonary toxicity will be communicated in Warnings and Precautions. The applicant did not submit a proposed REMS or risk management plan with this application. Given these are fatal diseases and the clinically meaningful activity of midostaurin, DRISK and the Division of Hematology Products (DHP) agree that a REMS is not necessary to ensure the benefits of midostaurin outweigh its risks.

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) Rydapt (midostaurin) is necessary to ensure the benefits outweigh its risks. Novartis submitted a New Drug Application (NDA) 207997 for midostaurin with two proposed indications. The first indication is for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 mutation positive as detected by an FDA-approved test. The second indication is for the treatment of aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL). This application is under review in the Division of Hematology Products (DHP).The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Rydapt (midostaurin), a new molecular entity (NME), is a kinase inhibitor proposed for treatment of adult patients with:[1]

- Newly diagnosed AML who are FLT3 mutation positive as detected by an FDA-approved test,in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. Midostaurin is not indicated as a single agent therapy for patients with AML.
- Aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL).

Midostaurin is prepared as a 25 mg capsule to be taken by the oral route. The dosage for AML is 50 mg twice daily, and for ASM/SM-AHN/MCL it is 100 mg twice daily.

Midostaurin is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for midostaurin (NDA 207997) relevant to this review:

- July 2009: Granted orphan status for treatment of patients with AML
- April 2010: Granted orphan status for treatment of patients with Mastocytosis
- January 20, 2016: Granted Fast Track designation for treatment of patients with Mastocytosis
- January 29, 2016: Granted Breakthrough Therapy designation for treatment of patients with AML.
- April 1, 2016: Rolling Review was granted.
- August 29, 2016: NDA 207997 submission received
- October 28, 2016: Priority Review was granted
- December 13, 2016: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that there are no safety concerns identified at this time, that would require a REMS. There are no plans for an Advisory Committee (AC) meeting.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Conditions

Acute Myeloid Leukemia (AML)

Acute Myeloid Leukemia (AML) is the most common type of acute leukemia in adults.[2] 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. Based on data from the National Cancer Institute, the estimated new cases and deaths from AML in the United States in 2016 were 21,380 and 10,590.[3] The incidence increases with age, with more than 50% of AML patients being over 60 years old.

Systemic Mastocytosis (SM)

SM is a heterogeneous group of rare, clonal disorders characterized by increased accumulation of abnormal mast cells in different tissues, including bone marrow, skin, the gastrointestinal (GI) tract, the liver, and the spleen. SM is comprised of indolent SM, smoldering SM, systemic mastocytosis with an associated hematological neoplasm (SM-AHN), aggressive systemic mastocytosis (ASM), and mast cell leukemia (MCL). Information about the epidemiology of this disease is scarce. In a recent population-based epidemiological study in Denmark, the incidence rates per 100,000 for ASM, SM-AHN, and MCL were 0.01, 0.04, and 0.01, respectively. Surveillance, Epidemiology, and End Results (SEER) data for these collective SM variants in the United States are consistent with the rates of Denmark study.[4] Median survival ranges are 3.5 years in patients with ASM, 2 years in patients with SM-AHM, and 2 months in patients with MCL.[5]

Patients with SM can suffer from a wide range of disabling symptoms that adversely affect their quality of life. Skin-related symptoms typically include pruritis, flushing and urticaria; other mediator-related symptoms include nausea, vomiting, diarrhea, abdominal pain, anaphylactoid reactions, anemia and coagulopathy. Advanced forms of the disease are characterized by organ dysfunction related mast cell infiltration. The organ systems typically involved are the bone marrow (cytopenias), liver (hepatomegaly, ascites, and increased liver enzymes), bones (osteolysis, pathologic fractures), spleen (splenomegaly) and the GI tract (malabsorption, weight loss).[5]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Acute Myeloid Leukemia (AML)

The treatment of AML is divided into two phases: remission induction and consolidation/maintenance. Remission induction chemotherapy is administered to produce a complete remission (CR) in the bone marrow. If a CR is achieved and no further therapy given, over 90% of patients will have a recurrence of AML in weeks to months. To prevent recurrence, intensive therapy, called consolidation, is given after recovery from remission induction therapy. Consolidation therapy can be accomplished with multiple courses of chemotherapy or high-dose chemotherapy with autologous or allogeneic stem cell transplantation.[2]

Overall, the results of treatment of AML in elderly patients remain unsatisfactory. Therefore, treatment results are generally analyzed separately for younger (18-60 years) patients and for older patients (>60 years). With current standard chemotherapy regimens, about 30-35% of younger patients survive longer than 5 years. For the past 3 decades, the standard therapy for younger patients with newly diagnosed AML has been the “7+3”remission induction regimen with cytarabine and daunorubicin, followed by high dose cytarabine for remission consolidation. In older patients, fewer than 10% survive over 5 years. Induction chemotherapy produces complete remission (CR) in most (50-70%) patients with AML, however between 50-80% of patients relapse within 1-2 years. Patients with AML succumb to their disease due to neutropenia-associated infections and/or thrombocytopenia-associated bleeding.

Patients with AML who have poor prognostic features are recommended to enroll into clinical trials and/or to undergo stem cell transplantation (SCT) following achievement of remission with standard

induction chemotherapy. Significant improvements in overall survival (OS) and disease free survival (DFS) for AML patients harboring FLT-3 mutations have been reported with allo-SCT compared to chemotherapy or autologous SCT.[2] However, these patients remain at high risk of relapse post-SCT compared to patients without FLT3 mutations, and therefore represent an unmet medical need for this patient population.

Systemic Mastocystosis (SM):

The only FDA approved drug to treat Aggressive Systemic Mastocytosis (ASM) is Gleevec (imatinib). Imatinib is approved to treat adult patients with ASM without the D816V c-Kit mutation as determined with an FDA-approved test or with c-Kit mutational status unknown.[6] Most cases of SM are associated with activating mutations in the Kit receptor tyrosine kinase, which acts as a receptor for Stem Cell Factor (SCF), the principal growth factor for mast cells. The most frequent activating mutant is D816V, which is detected in more than 90% of patients with SM. The D816V mutant is resistant to most tyrosine kinase inhibitors, including imatinib. Therefore, these patients which harbor this resistant mutation represent an unmet medical need.

The imatinib label has Warnings and Precautions regarding edema, cytopenia, congestive heart failure/left ventricular dysfunction, hepatotoxicity, grade 3 and 4 hemorrhage, GI perforations, cardiogenic shock, bullous dermatologic reactions, hypothyroidism, fetal harm, growth retardation occurring in children and pre-adolescents, tumor lysis syndrome, and reports of motor vehicle accidents. Imatinib does not have a Boxed Warning or REMS for any of these adverse events.

4 Benefit Assessment

Acute Myeloid Leukemia (AML)

Study 1 supporting midostaurin to treat AML, consisted of a double blind multicenter trial that enrolled 717 treatment-naïve AML patients (excluded patients who were older than 60 years old) with activating FLT-3 mutations.[1] Patients in both arms received standard induction (cytarabine and daunorubicin) and consolidation (high dose cytarabine) treatments. Patients in the midostaurin arm (n=355) received midostaurin 50 mg orally twice a day during chemotherapy and up to 12 additional 28-day cycles.. Patients in the placebo arm (n=354) received placebo on the same schedule as the midostaurin arm. The primary endpoint was Overall Survival (OS) and the secondary endpoint was Event Free Survival (EFS). The OS was 74.7 months in midostaurin arm and 25.6 months in placebo arm. The median EFS was 8.2 months in the midostaurin arm and 3 months in the placebo arm. The medical reviewer recommended approval based on the data from the OS findings.[8]

Systemic Mastocytosis (SM):

Study 2 supporting midostaurin to treat ASM, SM-AHN, or MCL (collectively referred to as advanced SM) consisted of an open-label and single-arm multicenter trial.[1] Study 2 enrolled adult patients who relapsed or progressed on 0, 1, or 2 prior regimens for SM. The study excluded patients with Serum

Creatinine (S.Cr) >2, hepatic transaminase >2.5x Upper Limit of Normal (ULN) (or >5x ULN if disease-related), total bilirubin >1.5x ULN (or >3 x ULN if disease-related), QTc >450 msec, cardiovascular disease including left-ventricular ejection fraction <50%, or any pulmonary infiltrates. Patients received midostaurin 100 mg orally twice daily until disease progression or intolerable toxicity. Of the 116 patients enrolled, 89 patients were eligible and constituted the primary efficacy population (PEP). The median age of PEP was 64 (from 25 to 82 years old). Of the 89 patients, 16 patients had ASM, 57 patients had SM-AHN, and 16 patients had MCL.

Efficacy was evaluated by the Overall Response Rate (ORR) by 6 cycles, as determined by a study steering committee using modified Valent criteria. Per modified Valent criteria, the ORR for ASM, SM-AHN, and MCL were 75%, 58%, and 50% respectively.

The sponsor also evaluated efficacy according to the 2013 International Working Group (IWG) criteria. The ORR for ASM, SM-AHN, and MCL were 31%, 11%, and 19% respectively. The medical reviewer concluded that the Applicant provided evidence of efficacy per both the modified Valent criteria and the IWG criteria.[7]

5 Risk Assessment

Pulmonary events such as pneumonitis and interstitial lung disease, some of which have been fatal, have been reported in both AML and SM patients. Per study 1 for AML, patients in the midostaurin arm who developed pleural effusion was 5.7%, and (b)(4) These results were similar to the placebo arm. Per study 2 for SM, patients who developed interstitial lung disease or pneumonitis was 2.1 %, and respiratory failure was 1.4%.[1]

Based on mechanism of action and findings in animal reproduction study, midostaurin can cause fetal harm when administered to a pregnant woman. There is no available data on midostaurin use in pregnant women. In animal reproduction studies, oral administration of midostaurin to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities, including late embryo-fetal death and reduced fetal birth weight, with delays in fetal growth at doses lower than the recommended human dose.[1] The following paragraph from Proposed Prescribing Information, Section 8.1 Animal Data describes more details regarding the teratogenicity of midostaurin in animal studies.

"During organogenesis, midostaurin administered at oral doses greater or equal to 3 mg/kg/day (approximately (b) (4) times the human exposure at the recommended dose by AUC) to pregnant female rats caused late embryofetal death. Reduced fetal birth weight (b) (4) effects on fetal growth (severe renal pelvic cavitation, (b) (4), and widened anterior fontanelle) were observed in the absence of maternal toxicity at the highest dose of 30 mg/kg/day (approximately 0.05 times the human exposure at the recommended dose by AUC). (b) (4) midostaurin (b) (4) administered to pregnant rabbits during organogenesis, maternal toxicity was (b) (4) with spontaneous abortions and some delay in fetal growth (reduced fetal birth weight, (b) (4)), (b) (4) at doses greater than or equal to 10 mg/kg/day (approximately 0.01 times the human exposure at the recommended dose by AUC)."

6 Expected Postmarket Use

During the AML induction and consolidation phases, midostaurin will be used in an inpatient setting.

To treat SM-AHN, ASM, and MCL, midostaurin will be used mostly at out-patient settings unless patients are admitted to hospitals.

Midostaurin will be primarily prescribed by oncologists/hematologists who are familiar with the management of chemotherapeutic toxicities such as pulmonary toxicity and embryo-fetal toxicity.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for midostaurin beyond routine pharmacovigilance and labeling. A Patient Information insert to accompany product labeling is proposed by the Applicant to provide patients with the information of the potential risk of (b)(4)

8 Discussion of Need for a REMS

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

The estimated population of AML patients with FLT3 mutation positive is about one third of 20,000 cases which is about 6,000-7,000 cases per year. With current standard chemotherapy regimens, fewer than 10% of older patients (>60 years) survive over 5 years. About 30-35% of younger patients (18-60 years) survive longer than 5 years. The presence of the FLT3 mutation is associated with a poorer prognosis that carries a more dismal outcome. In study 1, the overall survival (OS) was 74.7 months in midostaurin in midostaurin arm and 25.6 months in placebo arm. The median event free survival (EFS) was 8.2 months in midostaurin arm and 3 months in placebo arm. Clinical reviewers recommend approval based on the data from the OS findings.[8]

SM is an extremely rare disorder, the exact incidence is unknown. It is estimated that there are approximately 200 cases of ASM+SM-AHM+MCL in the United States per year. For MCL, the average survival time is 2 months. In study 2 the response rate was 50% per modified Valent Critera and 19% per IWG criteria.[1] The stable disease after 6 cycles (28 days per cycle) of treatment was 18.8%.[7] In study 2, for ASM, the response rate was 75% per modified Valent criteria and 31% per IWG criteria; for SM-AHN, the response rate was 58% per modified Valent criteria and 11% per IWG criteria. Based on these results, clinical reviewers recommend approval.

The risks of concern are pulmonary toxicity and embryo-fetal toxicity. Cases of interstitial lung disease and pneumonitis, some fatal, have occurred in patients treated with midostaurin as monotherapy or with chemotherapy. The risk of pulmonary toxicity will be communicated in the Warnings and Precautions section of the label.[1]

Seven days of cytarabine plus 3 days of anthracycline (7+3) is the standard chemotherapy regimen to treat patients with AML and has been used during the 2nd and 3rd trimester of pregnancy. Since midostaurin carries the risk of embryo-fetal toxicity, the cross disciplinary review team is concerned about midostaurin potentially being added to 7+3 to treat pregnant patients who have FLT3 positive AML. There was also concerned about the potential chronic administration to treat patients with SM, who may be of child bearing potential.

The risk of embryo-fetal toxicity of midostaurin is based on non-clinical data in rats and rabbits that resulted in late term embryo-fetal loss and varying effects on fetal growth, and birth defects. These effects were observed at doses lower than the recommended human dose.

Cytarabine, daunorubicin and idarubacin are examples of drugs used to treat AML, their labelings include the risk of embryo fetal toxicity. The professional labeling of cytarabine indicates use in pregnancy is Category D. Women of childbearing potential should be advised to avoid becoming pregnant. There is a warning in daunorubicin labeling that daunorubicin may cause fetal harm when administered to a pregnant woman. The labeling of idarubicin includes use in pregnancy is Category D. Women of childbearing potential should be advised to avoid pregnancy. These labelings were approved before the Pregnancy and Lactation Labeling Rule (PLLR) went into effect on June 30, 2015. Per PLLR, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule.

Vesanoid (tretinoin) capsules are indicated for the induction of remission in patients with acute promyelocytic leukemia (APL), characterized by the presence of the t(15;17) translocation and/or the presence of the PML/RARα gene who are refractory to, or who have relapsed from, anthracycline chemotherapy, or for whom anthracycline-based chemotherapy is contraindicated. Vesanoid professional labeling includes a box warning for teratogenicity.

Thalidomide and related analog's (lenalidomide, pomalidomide) professional labeling includes a box warning and each product requires a REMS to mitigate the risk of teratogenicity. Reproduction studies in animals and data from pregnant women have shown evidence of fetal abnormalities with thalidomide. Thalidomide is contraindicated for use in women who are pregnant. As stated in the label, even a single dose taken by a pregnant woman during her pregnancy can cause severe birth defects.

At this time, imatinib is the only drug currently approved by the FDA with an indication for the treatment of Aggressive Systemic Mastocytosis (ASM) without the D816V c-kit mutation, and 90% of patients have this resistant mutation. This leaves significant population of approximately 90% of patients that still require treatment. The risk of fetal harm for imatinib is based on data from non-clinical studies. This risk is communicated in warnings and precautions, section 5.10 and use in specific populations, section 8.1 of labeling.

The embryo-fetal toxicity of midostaurin is demonstrated in the animal studies. There is no available data on midostaurin use in pregnant women. If approved, midostaurin proposed indication is in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.

Midostaurin is not indicated as a single agent therapy for patients with AML. Because of the concerns that cytarabine and daunorubicin 7+3 may be used to treat patients who are pregnant in their 2nd and 3rd trimester and, the potential chronic administration of midostaurin to treat patients with SM, who may be of child bearing potential, DPMH (Division of Pediatric and Maternal Health),[9] DRISK, and DHP supported a box warning for the risk of fetal-embryo toxicity.

In the midostaurin clinical trials, the drug showed clinical benefit for both AML and SM. In addition, these patients will likely be managed by oncologists who are generally aware of the fetal toxic effects of chemotherapeutic agents, and how to properly inform/counsel patients of this risk. The clinical reviewers recommend approval of midostaurin on the basis of the efficacy and safety information currently available.

The serious risks associated with midostaurin include pulmonary toxicity and nonclinical findings of embryo-fetal abnormalities and embryo-fetal death. The risk of embryo-fetal toxicity will be included in the label as a boxed warning, while pulmonary toxicity will be communicated in Warnings and Precautions. Given these are fatal diseases and the clinically meaningful activity of midostaurin, DRISK and the Division of Hematology Products (DHP) agree that a REMS is not necessary to ensure the benefits of midostaurin outweigh its risks.

9 Conclusion & Recommendations

Based on the available data, DRISK and DHP agree that a REMS is not necessary for midostaurin to ensure the benefits outweigh the risks. Should DHP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK so that the risk: benefit analysis can be reevaluated.

10 References

1. Proposed Prescribing Information for midostaurin (NDA 207997) February 6, 2017
2. AML Pathophysiology and Treatment, www.emedicine.medscape.com, accessed January 12, 2017.
3. www.cancer.gov/types/leukemia, accessed January 23, 2017
4. Novartis. Summary of Clinical Safety for Midostaurin, August 19, 2016.
5. Systemic Mastocytosis, www.emedicine.medscape.com, accessed January 12, 2017.
6. Gleevec Prescribing Information, August 2016.
7. Kasamon, Y. DHP, mid-cycle clinical review of midostaurin (NDA 207997) for Advanced SM, November 30, 2016.

8. Ward, A. DHP, mid-cycle clinical review of midostaurin (NDA 207997) for FLT3 positive newly diagnosed AML, November 30, 2016.

9. Liedtka, J. DPMH, Pregnancy and Lactation Labeling Review of midostaurin (NDA 207997), January 27, 2017.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MEI-YEAN T CHEN
02/13/2017

CYNTHIA L LACIVITA
02/13/2017
Concur