CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211349Orig1s000

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	211349
PDUFA Goal Date	November 29, 2018
OSE RCM #	2018-640; 2018-642
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	November 13, 2018
Subject	Review to determine if a REMS is necessary
Established Name	Gilteritinib
Trade Name	Xospata
Name of Applicant	Astellas Pharma Global Development Inc.
Therapeutic Class	Tyrosine Kinase Inhibitor
Formulation(s)	40 mg tablet
Dosing Regimen	120 mg orally once-daily

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 gilteritinib (Xospata) is necessary to ensure the benefits outweigh its risks. Astellas Pharma Global Development Inc. submitted a New Drug Application (NDA) 211349 for gilteritinib with the proposed indication for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test. The serious risks associated with gilteritinib are posterior reversible encephalopathy syndrome (PRES), QT interval prolongation, pancreatitis and embryo-fetal toxicity. The applicant did not submit a REMS with this application but proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information, and a Patient Package Insert (PPI).

DRISK and the Division of Hematology Products (DHP) have determined that if approved, a REMS is not necessary to ensure the benefits of gilteritinib 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. Despite the availability of new therapies, the long-term prognosis for patients with R/R AML remains limited and there is a clear need for new treatments for patients with relapsed or refractory AML with a FLT3 mutation. In the clinical trial, gilteritinib appeared efficacious in both its primary and secondary outcomes. The most concerning adverse reactions associated with the use of gilteritinib are PRES, QT interval prolongation, pancreatitis and embryo-fetal toxicity; if approved, these risks will be communicated in the Warnings and Precautions section of the product label as well as in section 17, Patient Counseling Information, and in the PPI to inform patients, increase the prominence of this information, and promote its mitigation.

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) gilteritinib (Xospata) is necessary to ensure the benefits outweigh its risks. Astellas Pharma Global Develoment Inc. submitted a New Drug Application (NDA) 211349 for gilteritinib with the proposed indication for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.[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 Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information, and a Patient Package Insert (PPI).

2 Background

2.1 PRODUCT INFORMATION

Gilteritinib is a NME NDA type 505(b)(1) pathway application.[a] It is a FLT3 tyrosine kinase inhibitor, proposed for indication as treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test. Gilteritinib demonstrated the ability to inhibit FLT3

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

receptor signaling and proliferation in cells exogenously expressing FLT3 including FLT3-ITD, tyrosine kinase domain mutations (TKD) FLT3-D835Y and FLT3-ITD-D835Y, and it induced apoptosis in leukemic cells expressing FLT3-ITD.[1,2] Gilteritinib is prepared as 40 mg tablets to be taken by the oral route. The recommended dose of gilteritinib is 120 mg taken orally once-daily with or without food. Gilteritinib should be interrupted for Grade 3 or greater toxicity considered related to the drug and resumed at a reduced dose when the toxicity resolves or improves to Grade 1.[b] The daily dose can be reduced from 120 mg to 80 mg.[1] Gilteritinib was granted orphan drug designation on July 13, 2017, and fast track designation on October 4, 2017. Gilteritinib is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for gilteritinib (NDA 211349) relevant to this review:

- 06/07/2013: Investigation New Drug (IND) 117548 submission was received.
- 07/13/2017: Orphan Drug designation granted.
- 10/04/2017: Fast track designation granted.
- 03/29/2018: NDA 211349 submission for gilteritinib with the proposed indication for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test, received.
- 07/23/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that safety review is ongoing and at this time, the review teams have not identified a need for a REMS for gilteritinib.

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.[4,5] 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

[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 (B): *The seriousness of the disease or condition that is to be treated with the drug.*

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.[3] 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%).[3] 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.[5] 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.[8] Older patients fare less well, with CR rates of approximately 50% and 2-year overall survival of approximately 20%.[9]

Patients who are fit for intensive therapy should receive a salvage chemotherapy regimen followed by hematopoietic stem cell transplant (HSCT). About half will achieve a second complete remission, and 5-year survival of patients who achieve a second remission is about 40%.[10] 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[11], midostaurin (Rydapt) for the treatment of patients with newly diagnosed AML with FLT3 mutations[12]; daunorubicin and cytarabine (Vyxeos) for the treatment of newly diagnosed therapy-related AML or AML with myelodysplasia-related changes[13]; 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 responded to initial treatment (refractory)[14]; and in 2018, ivosidenib (Tibsovo) for the treatment of IDH1-mutated relapsed or refractory (R/R) AML[15].

Mutational status of FLT3, a member of the class III receptor tyrosine kinase, is now well recognized as delineating a subtype of leukemia with a poor prognosis. There are known mutations in FLT3 that appear to be self-activating. Two of these mutations are well described in the literature: an internal

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

tandem duplication (ITD) in the juxtamembrane domain of FLT3 that is present in 28% to 34% of AML cases and a TKD mutation at around D835 in the activation loop of FLT3, which is present in 11% to 14% of AML cases.[16] Patients with FLT3-ITD mutation show poor prognosis in clinical studies, with a higher relapse rate, a shorter duration of remission from initial therapy (6 months vs 11.5 months for those without FLT3-ITD mutations), as well as reduced disease-free survival (DFS) (16% to 27% vs 41% at 5 years) and overall survival (OS) (15% to 31% vs 42% at 5 years).[17,18,19,20,21] The incidence of relapse after HSCT is also higher for patients with FLT3-ITD (30% vs 16% at 2 years for those without FLT3-ITD mutations).[22] Older patients with FLT3-ITD are particularly at risk. In a study of AML patients with intermediate cytogenetic risk treated with initial induction/consolidation chemotherapy with or without HSCT, FLT3-ITD negative patients who were younger than the median age of the study (47 years) had a 6-year OS rate of 56%, and FLT3-ITD positive patients older than the median age had a 6-year OS of 6%.[23] Despite the availability of new therapies, the long-term prognosis for patients with R/R AML remains limited and there is a clear need for new treatments for patients with relapsed or refractory AML with a FLT3 mutation.

4 Benefit Assessment

The efficacy of gilteritinib was evaluated in an open-label, randomized, multicenter and double-blind clinical trial (ADMIRAL trial, NCT02421939). The study population included 142 adult patients with relapsed or refractory AML and a FLT3-ITD, D835 or I836 mutation by the LeukoStrat CDx FLT3 Mutation Assay.

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 gilteritinib. Efficacy was established on the basis of the rate of complete remission (CR)/complete remission with partial hematologic recovery (CRh), the duration of CR/CRh (DOR), and the rate of conversion from transfusion dependence to transfusion independence in each of these studies. The median follow-up was 4.7 months (95% CI: 2.9, 16.1). For patients who achieved a CR/CRh, the median time to first response was 2 months (range, 0.9 to 9.7 months). The CR/CRh rate was 31 of 126 in patients with FLT3-ITD or FLT3-ITD/TKD and 0 of 12 in patients with FLT3-TKD only. The efficacy results are shown in Table 1.[1,24,e] Among the 107 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 34 (31.8%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. For the 34 patients who were independent of both RBC and platelet transfusions at baseline, 18 (52.9%) remained transfusion-independent during any 56-day post-baseline period.

Table 1: Efficacy Results in Patients with Relapsed or Refractory AML [1,24,e]

Remission Rate	ADMIRAL

[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.*

	Gilteritinib (120 mg daily) N=142
CR*/CRh† n/N (%)	31/142 (21.8)
95% CI‡	15.3, 29.5
Median DOR§ (months)	4.5
Range (months)	0.1 to 16.1¶
CR* n/N (%)	18/142 (12.7)
95% CI‡	7.7, 19.3
Median DOR§ (months)	8.7
Range (months)	0.6 to 14
CRh† n/N (%)	13/142 (9.2)
95% CI‡	5.0, 15.1
Median DOR§ (months)	2.9
Range (months)	0.1 to 16.1¶

CI: confidence interval; NE: not estimable; NR: not reached; Only responses prior to HSCT were included in response rate.

*CR was defined as an absolute neutrophil count ≥1.0 x 10^9/L, platelets ≥100 x 10^9/L, normal marrow differential with <5% blasts, must have been red blood cells, platelet transfusion independent and no evidence of extramedullary leukemia.

†CRh was defined as marrow blasts <5%, partial hematologic recovery absolute neutrophil count ≥0.5 x 10^9/L and platelets ≥50 x 10^9/L, no evidence of extramedullary leukemia and could not have been classified as CR.

‡The 95% CI rate was calculated using the exact method based on binomial distribution.

§DOR was defined as the time from the date of either first CR or CRh until the date of a documented relapse of any type. Deaths were counted as events.

¶Response was ongoing.

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 gilteritinib. The safety analysis of gilteritinib primarily focuses on 292 adult patients with relapsed or refractory AML treated with 120 mg gilteritinib daily. The integrated R/R AML safety population included a total of 444 patients who received at least 1 dose of gilteritinib and included 252 patients from Study 2215-CL-0101, 24 patients from Study 2215-CL-0102 and 168 patients from Study 2215-CL-0301. Of those, 66 patients received gilteritinib <120 mg, 241 patients received gilteritinib 120 mg (including 168 patients from Study 2215-CL-0301) and 137 patients received gilteritinib > 120 mg as the initial dose. The median duration of exposure to gilteritinib was 3 months (range 0.1 to 42.8 months).

Deaths

There were total of 175 grade 5 events which are classified by system organ class (SOC) as follows: blood and lymphatic system disorders (n=3), cardiac disorders (n=10), gastrointestinal disorders (n=4), general disorders and administration site conditions (n=11), infections and infestations (n=43), injury, poisoning, procedural complications (n=1), metabolism and nutrition disorders (n=2), neoplasms (n=64), nervous system disorders (n=8), renal and urinary disorders (n=2), respiratory, thoracic and mediastinal (n=17), and vascular disorders (n=1). All grade 5 neurological events were bleeding, and all in neoplasm SOC were acute leukemia. Out of 175 total events, 14 events were grouped under broad standardized MedDRA queries (SMQ) for Torsades de pointes (TdP).[24] Six events were due to multi-organ failure, four

events were cardiac arrest, two were definitively due to ventricular arrhythmias (one each ventricular tachycardia and ventricular fibrillation), and one of each as sudden death and loss of consciousness.[f]

Serious Adverse Events (SAE)

The most frequent non-hematological serious adverse reactions (≥5%) reported in patients were pneumonia (22%), transaminase increased (15%), hemorrhage (11%), sepsis (20%), dyspnea (7%), hypotension (7%), hypersensitivity (7%), syncope/falls (6%), encephalopathy/delirium (6%), fungal infections (6%), hypertension (6%), myalgia/arthralgia (5%), bilirubin increase (5%), fatigue/malaise (5%), and fever (5%). Overall, 29 of 292 patients (10%) permanently discontinued gilteritinib treatment due to an adverse reaction. The most common adverse reactions leading to discontinuation were cardiac arrest/ventricular arrhythmias (1%), transaminase elevation (1%), and dyspnea/respiratory failure (1%). The most common adverse reactions (≥20%) were myalgia/arthralgia (42%), transaminase increase (40%), fatigue/malaise (40%), fever (35%), non-infectious diarrhea (34%), dyspnea (34%), edema (34%), rash (30%), nausea (27%), stomatitis (26%), pneumonia (26%), cough (25%), sepsis (22%), headache (21%), hypotension (21%), dizziness (20%) and vomiting (20%). Other clinically significant adverse reactions occurring in ≤10% of patients included: electrocardiogram QT prolonged (7%), cardiac failure[g] (4%), pericardial effusion (3%), pericarditis (2%), differentiation syndrome (1%) and posterior reversible encephalopathy syndrome (1%).[1]

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

5.1 POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES)

In the clinical trial, in the gilteritinib 120 mg group, 1.7% (4/241) of patients experienced delirium, 0.4% (1/241) of patients experienced encephalopathy and 0.8% (2/241) of patients experienced PRES. Overall, 2.0% (9/444) of patients in the gilteritinib total group experienced delirium, 0.9% (4/444) of patients experienced encephalopathy and 0.7% (3/444) of patients experienced PRES.[26] There have been rare reports of PRES with symptoms including seizure and altered mental status with gilteritinib. Symptoms have resolved after discontinuation of gilteritinib. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). To mitigate this risk, labeling instructs prescribers to discontinue gilteritinib in patients who develop PRES.[1] The risk of PRES will likely be communicated in the Warnings and Precautions.

5.2 PROLONGED QT INTERVAL

In patients who received at least 1 dose gilteritinib (n = 444), 7.4% (33/444) patients experienced QT prolongation, 5.2% (23/444) patients experienced syncope, 1.1% (5/444) patients experienced cardiac arrest and 0.5% (2/444) patients experienced loss of consciousness. Sudden death, ventricular arrhythmia, ventricular fibrillation and ventricular tachycardia were experienced by 1 (0.2%) patient in each TEAE category. The FDA QTcF categorical analysis stated that a total of 12/447 (2.7%) subjects from 3 studies (<120 mg [n=65], 120 mg [n=242], and >120 mg [n=140]) had a maximum post-baseline QTcF

[f] Pulte E to Olickal T. (Internal communication from clinical reviewer to DRISK), dated July 11, 2018.

[g] Grouped terms include ejection fraction decreased, cardiac failure, cardiac failure congestive, pulmonary edema, acute pulmonary edema, chronic left ventricular failure and hepatic congestion[1]

>500 msec. These 12 subjects were distributed equally among the 3 dose-pooled groups: <120 mg, 120 mg and >120 mg. A total of 30 (7.1%; n=423) subjects from 3 studies had a maximum post-baseline ΔQTcF >60 msec. Seventeen subjects (7.1%; n=238) had a maximum post-baseline ΔQTcF >60 msec at 120 mg in study. Cardiac arrest, loss of consciousness, ventricular fibrillation and ventricular tachycardia were experienced by ≤ 3/241 (1.2%) of patients and no patients in the gilteritinib 120 mg group experienced sudden death or ventricular arrhythmia (see the Table 2 in the Appendix).[25] The risk of QT prolongation will likely be communicated in the Warnings and Precautions sections of the label. Monitoring and dosage modifications for toxicities to address the safety issues with gilteritinib will likely be included in the Dosage and Administration section of the label.

5.3 PANCREATITIS

There have been rare reports of pancreatitis in patients receiving gilteritinib in clinical studies. Labeling instructs to evaluate patients who develop signs and symptoms of pancreatitis and to interrupt and reduce the dose of gilteritinib in patients who develop pancreatitis. The risk of pancreatitis 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 gilteritinib will likely be included in the Dosage and Administration section of the label.

5.4 EMBRYO-FETAL TOXICITY

Similar to other tyrosine kinase inhibitors, based on findings in animals and its mechanism of action, gilteritinib can cause embryo-fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of gilteritinib to pregnant rats during organogenesis caused embryo-fetal deaths and abnormalities at maternal exposures (AUC) approximately 0.4 times the AUC in patients receiving the recommended dose. Advise females of reproductive potential to use effective contraception during treatment with gilteritinib and for at least 6 months after the last dose of gilteritinib. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception during treatment with gilteritinib and for a specified time, dependent on the patient's sex, after the last dose will be communicated in the Use in Specific Populations section of the label.[1]

5.5 OTHER SERIOUS ADVERSE EVENTS (SAE)

Differentiation Syndrome (DS)

There have been rare reports of DS in patients receiving gilteritinib in clinical studies. Overall, 0.7% (3/444) of patients in the gilteritinib total group experienced acute promyelocytic leukemia differentiation syndrome.[26] The risk of DS will likely be communicated in the Adverse Reactions section of the label. Additionally, the applicant will be required to conduct a post-marketing required (PMR) study to characterize gilteritinib-related DS (including incidence, observed signs and symptoms, duration, and response to intervention) based on patient-level data from on-going trials in patients with AML.[27,28]

6 Expected Postmarket Use

The proposed indication is for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation. It is expected that oncologists/hematologists, who should be familiar with the management of chemotherapeutic toxicities such as PRES, QT prolongation, pancreatitis, and embryo-fetal toxicity, will be the likely prescribers of gilteritinib in both inpatient and outpatient settings.

7 Risk Management Activities Proposed by the Applicant

The applicant did not propose any risk management activities for gilteritinib beyond routine pharmacovigilance and labeling. The applicant proposed Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information, and a PPI, to inform patients regarding the potential risks of PRES and QT prolongation.

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 gilteritinib, DRISK considers patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population.

Gilteritinib is a tyrosine kinase inhibitor, proposed for indication as treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation. Based on the efficacy and safety information currently available, the clinical reviewers stated that gilteritinib shows clinical meaningful benefit to patients with AML, and recommends approval of gilteritinib for the treatment of adult patients with relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test.[29]

DRISK and DHP have determined that if approved, a REMS is not necessary to ensure the benefits of gilteritinib outweigh its risks. Labeling, including Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with gilteritinib. The most concerning adverse reactions observed with the use of gilteritinib are PRES, QT prolongation, pancreatitis, and embryo-fetal toxicity. Gilteritinib 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. Despite the availability of new therapies, the long-term prognosis for patients with R/R AML remains limited and there is a clear need for new treatments for patients with relapsed or refractory AML with a FLT3 mutation.

Ivosidenib, an IDH1 inhibitor proposed for indication as treatment of adult patients with relapsed or refractory AML with an IDH1 mutation was approved July 2018. 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. The risk of QTc interval prolongation for ivosidenib is communicated in the Warnings and Precautions section of the label.

Of the 242 patients treated with gilteritinib in the clinical trial, 1.7% (4/242) were found to have a QTc greater than 500 msec (Grade ≥3) and 7.1% (17/238) of patients had an increase from baseline QTc greater than 60 msec. The recommended dose of gilteritinib is 120 mg taken orally once-daily. No patients in the gilteritinib 120 mg group experienced sudden death or verntricular arrhythmia. The risks of PRES, QT prolongation, pancreatitis, and embryo-fetal toxicity will likely be communicated in the

Warnings and Precautions section of the label; Patient Counseling Information in Section 17, as well as a PPI will be used to inform patients regarding the potential risks of PRES, QT prolongation, and pancreatitis, and will increase the prominence of this information and promote its mitigation. Monitoring and dosage modifications for toxicities to address the safety issues with gilteritinib will likely be included in the Dosage and Administration section of the label. Due to the rare incidents of DS in patients receiving gilteritinib in clinical studies, the applicant will be required to conduct a PMR study to characterize gilteritinib-related DS; the risk of DS will likely be communicated in the Adverse Reactions section of the label. Additionally, the applicant will be required to conduct a PMR study to characterize the long-term safety of gilteritinib in patients with relapsed or refractory acute myeloid leukemia (AML).[28] At this time, none of these risks will receive a boxed warning in the label.

9 Conclusion & Recommendations

If approved, DRISK has determined that a REMS is not necessary to ensure the benefits outweigh the risks of gilteritinib. The management of the risks associated with gilteritinib 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

10 Appendices

Table 2: Arrhythmia Due to QT Prolongation – Integrated R/R AML Safety Population[26]

MedDRA (v19.1) Preferred Term	**Gilteritinib**				
	< 120 mg (N = 66)	**120 mg (N = 241)**	**> 120 mg (N = 137)**	**Total (N = 444)**	**2215-CL-0301 (N = 168)**
Overall, n (%)	**4 (6.1)**	**35 (14.5)**	**26 (19.0)**	**65 (14.6)**	**20 (11.9)**
Electrocardiogram QT prolonged	3 (4.5)	21 (8.7)	9 (6.6)	33 (7.4)	10 (6.0)
Syncope	0	10 (4.1)	13 (9.5)	23 (5.2)	6 (3.6)
Cardiac arrest	1 (1.5)	3 (1.2)	1 (0.7)	5 (1.1)	3 (1.8)
Loss of consciousness	0	1 (0.4)	1 (0.7)	2 (0.5)	0
Sudden death	0	0	1 (0.7)	1 (0.2)	0
Ventricular arrhythmia	0	0	1 (0.7)	1 (0.2)	0
Ventricular fibrillation	0	1 (0.4)	0	1 (0.2)	0
Ventricular tachycardia	0	2 (0.8)	1 (0.7)	1 (0.2)	2 (1.2)

Source: ISS/SCS Table 13.4.22.2
AML: acute myeloid leukemia; R/R: relapsed or refractory
Note: The search strategy for arrhythmias due to QT prolongation was SMQ broad term "torsade de pointes/QT prolongation."

11 References

[1] Proposed Prescribing Information for gilteritinib as currently edited by the FDA, last updated October 22, 2018.

[2] Astellas Pharma Global Development Inc. Clinical Overview for gilteritinib, dated March 29, 2018.

[3] Doehner H, Weisdorf DJ, Bloomfield CD. Acute Myeloid Leukemia. *N Engl J Med.* 2015 Sep 17;373(12):1136-52.

[4] Licht JD, Sternberg DW. The molecular pathology of acute myeloid leukemia. *Hematology Am Soc Hematol Educ Program.* 2005:137-142.

[5] De Kouchkovsky I, Abdul-Hay M. 'Acute myeloid leukemia: a comprehensive review and 2016 update'. *Blood Cancer J.* 2016;6(7):e441.

[6] What are the key statistics about acute myeloid leukemia? American Cancer Society. https://www.cancer.org/cancer/acute-myeloid-leukemia/about/key-statistics.html. Accessed August 8, 2018.

[7] Kumar CC. Genetic Abnormalities and Challenges in the Treatment of Acute Myeloid Leukemia. *Genes & Cancer.* 2011;2(2):95-107.

[8] Fernandez HF, Sun Z, Yao X, et al. Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med.* 2009;361(13):1249-1259.

[9] Estey E, Dohner H. Acute myeloid leukaemia. *Lancet.* 2006;368(9550):1894-1907.

[10] Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood.* 2017;129(4):424-447.

[11] Idhifa. Prescribing Information (last updated 08/2017).

[12] Rydapt. Prescribing Information (last updated 04/2017).

[13] Vyxeos. Prescribing Information (last updated 08/2017).

[14] Mylotarg. Prescribing Information (last updated 04/2018).

[15] Tibsovo. Prescribing Information (last updated 07/2018).

[16] Schlenk RF, Dohner K. Impact of new prognostic markers in treatment decisions in acute myeloid leukemia. *Curr Opin Hematol.* 2009;16(2):98-104.

[17] Patel JP, Gonen M, Figueroa ME, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med.* 2012;366(12):1079-1089.

[18] Gale RE, Green C, Allen C, et al. The impact of FLT3 internal tandem duplication mutant level, number, size, and interaction with NPM1 mutations in a large cohort of young adult patients with acute myeloid leukemia. *Blood.* 2008;111(5):2776-2784.

[19] Yanada M, Matsuo K, Suzuki T, Kiyoi H, Naoe T. Prognostic significance of FLT3 internal tandem duplication and tyrosine kinase domain mutations for acute myeloid leukemia: a meta-analysis. *Leukemia.* 2005;19(8):1345-1349.

[20] Tiesmeier J, Muller-Tidow C, Westermann A, et al. Evolution of FLT3-ITD and D835 activating point mutations in relapsing acute myeloid leukemia and response to salvage therapy. *Leuk Res.* 2004;28(10):1069-1074.

[21] Moreno I, Martin G, Bolufer P, et al. Incidence and prognostic value of FLT3 internal tandem duplication and D835 mutations in acute myeloid leukemia. *Haematologica.* 2003;88(1):19-24.

[22] Brunet S, Labopin M, Esteve J, et al. Impact of FLT3 internal tandem duplication on the outcome of related and unrelated hematopoietic transplantation for adult acute myeloid leukemia in first remission: a retrospective analysis. *J Clin Oncol.* 2012;30(7):735-741.

[23] Wagner K, Damm F, Thol F, et al. FLT3-internal tandem duplication and age are the major prognostic factors in patients with relapsed acute myeloid leukemia with normal karyotype. *Haematologica.* 2011;96(5):681-686.

[24] Pulte E. Mid-Cycle Meeting, dated July 9, 2018.

[25] Johannesen L, Ng MJ, Huang D, Rahman MA, Li MY and Garnett CE. Interdisciplinary Review Team for QT Studies Consultation: QT Study Review, dated July 6, 2018.

[26] Astellas Pharma Global Develoment Inc. Summary of Clinical Safety for gilteritinib, dated March 29, 2018.

[27] Late-Cycle Meeting Minutes, dated September 27, 2018.

[28] FDA labeling revisions to the prescribing information (PI) and the PMR-PMC document, dated October 24, 2018.

[29] FDA Internal Wrap-Up Meeting, dated October 23, 2018.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TILL OLICKAL
11/13/2018

ELIZABETH E EVERHART
11/13/2018
I concur

CYNTHIA L LACIVITA
11/13/2018