CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210656Orig1s000

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	210656
PDUFA Goal Date	November 27, 2018
OSE RCM #	2018-891
Reviewer Name(s)	Joyce Weaver, Pharm.D.
Team Leader	Elizabeth Everhart, MSN, ACNP
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	Draft, September 12, 2018
Subject	Evaluation of Need for a REMS
Established Name	Glasdegib
Trade Name	Daurismo
Name of Applicant	Pfizer
Therapeutic Class	Hedgehog pathway inhibitor
Formulation(s)	Oral tablets
Dosing Regimen	100 mg orally once daily

Table of Contents

EXECUTIVE SUMMARY 3

1 Introduction 3

2 Background 3

2.1 Product Information 3

2.2 Regulatory History 4

3 Therapeutic Context and Treatment Options 4

3.1 Description of the Medical Condition 4

3.2 Description of Current Treatment Options 5

4 Benefit Assessment 5

5 Risk Assessment & Safe-Use Conditions 5

5.1 Embryo-Fetal Toxicity 5

5.2 QTc Interval Prolongation 5

6 Expected Postmarket Use 6

7 Risk Management Activities Proposed by the Applicant 6

8 Discussion of Need for a REMS 6

9 Conclusion & Recommendations 7

10 Appendices 8

10.1 References 8

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) glasdegib is necessary to ensure the benefits outweigh its risks. Pfizer submitted a New Drug Application (NDA 210656) for glasdegib with the proposed indication (b) (4)

The risks associated with glasdegib include embryo-fetal toxicity and QTc interval prolongation. The applicant did not submit a proposed REMS or risk management plan with this application.

Should glasdegib be approved, DRISK has concluded that a REMS is not needed to ensure its benefits outweigh its risks. Embryo-fetal toxicity is known to occur with this class of drugs, and is, therefore, already known to potential prescribers. The QTc interval prolongation that occurs with glasdegib can be managed with labeling.

DRISK and the Division of Hematology Products (DHP) agree that the safety profile for glasdegib is acceptable for the patient population, and healthcare providers who will prescribe and administer cemiplimab are likely to be able to manage the glasdegib-emergent adverse events without additional risk mitigation measures beyond labeling.

1 Introduction

This review by the DRISK evaluates whether a REMS for the NME glasdegib is necessary to ensure the benefits outweigh its risks. Pfizer submitted NDA 210656 for glasdegib with the proposed indication (b) (4)

[a] This application is under review in DHP. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Glasdegib, a new molecular entity[b], is a hedgehog pathway inhibitor. Abnormal hedgehog pathway signaling has been identified in leukemia stem cells. Preclinical studies have shown that Smoothened (SMO) inhibition may sensitize leukemic cells to cytarabine and other agents. The combination of glasdegib and cytarabine is directed at reducing therapeutic resistance and thus preventing persistence or progression of cancer. Glasdegib is proposed, in combination with low-dose cytarabine, for the treatment of newly-diagnosed AML in adults.

[a] During FDA review of the application, the proposed indication statement was changed to, in combination with low-dose cytarabine, for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults.

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

Glasdegib will be supplied as 100 mg and 25 mg tablets. Glasdegib will be administered 100 mg once daily orally, in combination with cytarabine 20 mg subcutaneously twice daily for 10 consecutive days of each 28-day cycle until disease progression or unacceptable toxicity.[c]

Glasdegib was granted orphan drug status for AML (June 28, 2017) and for MDS (October 20, 2017).

Glasdegib is not approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761097 relevant to this review:

- 06/28/2017: orphan status granted for AML
- 07/24/2017: Pre-NDA meeting; REMS not discussed
- 6/22/2018: Priority review granted; PDUFA 12/27/18
- 8/8/2018: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference; the Division indicated that there were no major safety concerns identified and a REMS was likely not needed

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

AML describes a group of heterogeneous hematopoietic stem cell disorders characterized by incomplete maturation of blood cells and reduced production of other normal hematopoietic cells. AML is most common in patients ≥ 65 years of age and has a slightly higher incidence in men compared to women.

Potential risk factors for AML include exposure to ionizing radiation, chemicals known to cause DNA damage (e.g., alkylating agents and drugs targeting topoisomerase II), and multiple predisposing conditions including myelodysplastic processes or other chronic bone marrow stem cell disorders.

The 5-year survival rate for adults with AML is approximately 24%.

About 19,520 people in the United States are diagnosed with AML each year, and more than 10,000 die yearly from the disease. AML makes up 32% of all adult leukemia cases. [1,d,e]

---

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

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

[e] 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.*

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

AML treatment options include cytarabine plus idarubicin, daunorubicin, or mitoxantrone, 5-azacytidine, decitabine, and hematopoietic cell transplantation. Supportive care includes transfusion support and/or hydroxyurea.[2]

4 Benefit Assessment[3,f]

The efficacy of glasdegib was examined in a phase 2 multi-center, randomized, open-label trial in patients AML (n=116).[4] Patients were randomized 2:1 to receive glasdegib 100 mg orally daily with cytarabine 20 mg subcutaneously twice daily on days 1 to 10 of a 28-day cycle, or cytarabine alone. Treatment continued until disease progression or unacceptable toxicity. The patients were mostly male (72%), and elderly (median age 76 years, range 58 to 92 years).

The primary efficacy measure was overall survival from the date of randomization to death from any cause. The median survival in the glasdegib group was 8.3 months (95% CI, 4.7, 12.2) compared with 4.3 months (95% CI, 1.9, 5.7) in the cytarabine alone group, p-value, 0.0002.

5 Risk Assessment & Safe-Use Conditions[5, g]

The safety database comprised data from 84 patients who received glasdegib in the AML clinical trial.

The most important serious adverse reactions are embryo-fetal toxicity and QTc interval prolongation.

5.1 EMBRYO-FETAL TOXICITY

Section 5.1 of the draft labeling describes the potential, based on mechanism of action and findings from animal embryo-fetal developmental toxicity studies, for embryo-fetal toxicity. Based on this, glasdegib is believed to cause severe birth defects and embryo-fetal death. The draft labeling advises healthcare providers to verify pregnancy status in female patients of reproductive potential, and to advise female patients of reproductive potential regarding contraception. Male patients should be advised to use effective contraception and condoms to avoid exposure to female partners who could become pregnant. A boxed warning is used in the labeling to describe the risk of embryo-fetal toxicity.

5.2 QTC INTERVAL PROLONGATION

The clinical trial excluded patients with baseline QTc greater than 470 msec and patients with history of long QT syndrome or uncontrolled cardiovascular disease. In clinical testing, one patient each developed ventricular fibrillation and ventricular tachycardia attributed to glasdegib.

---

[f] 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.*

[g] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

QTc interval prolongation was reviewed by the Interdisciplinary Review Team for QT studies. The review states the following[6]:

> Glasdegib prolongs the QTc interval in a dose/concentration-dependent manner; however, the mean QTc increase at the high clinical exposure scenario is less than 20 ms. Nonclinical data shows that glasdegib inhibits the hERG potassium channel and prolongs the QTc interval in dogs. Patients in clinical trials experienced QTc prolongation. In the S1 cohort of study B1371013, 5 (6%) patients in the glasdegib 100 mg + LDAC arm and 2 (12%) in the LDAC arm had QTcF values >500 ms. In the glasdegib + LDAC arm, 3 of the 5 patients also had an increase from baseline >60 ms. These cases are confounded by other risk factors that could also prolong the QTc interval such as concomitant use of other QT prolonging drugs or CYP3A4 inhibitors, and the presence of electrolyte abnormalities. Because glasdegib prolongs the QTc interval, we suggest that the findings of the thorough QT study are described in section 12.2 (Phamacodynamics) and the potential risk for patients taking CYPA3 inhibitors and other QT prolongers are described in section 5.2 (Warnings and Precautions).

As advised by the QT IRT Team review, the draft labeling describes the risk of QTc interval prolongation in section 5.2. The draft labeling advises healthcare providers to monitor patients for QTc prolongation, interrupt glasdegib therapy for QTc over 480 msec, and permanently discontinue for QTc prolongation with signs or symptoms of life-threatening arrhythmias.

6 Expected Postmarket Use

Glasdegib is likely to be used in both inpatient and outpatient healthcare setting. Because glasdegib will be taken orally, patients will be able to take glasdegib at home.

The patient population likely to receive glasdegib will be older patients (most patients in clinical testing were in excess of 65 years of age) with AML. Patients would be expected to be able to report their treatment-emergent signs and symptoms to their health care providers, and to undergo appropriate laboratory testing.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for glasdegib beyond professional labeling.

8 Discussion of Need for a REMS

The Clinical Reviewer believes the data support a favorable benefit:risk assessment for glasdegib for the treatment of adult patients with newly diagnosed AML because the overall survival primary efficacy endpoint was met in the clinical trial, and glasdegib + low-dose cytarabine was superior to low-dose cytarabine alone with respect to overall survival and complete remission. The Clinical Reviewer's

preliminary finding was that the application was appropriate for regular approval, with a boxed warning for embryo-fetal toxicity, and a warning (not boxed) for QT prolongation.[h]

The division has advised that the data do not support the need for a REMS. Embryo-fetal toxicity associated with glasdegib is a known effect of the class of drugs and the patient population likely to receive glasdegib will be older patients with AML. The clinical reviewer agrees with the applicant that a boxed warning in the labeling is sufficient to address the risk of embryo-fetal toxicity.

QTc interval prolongation was reviewed by the Interdisciplinary Review Team for QT studies. The review recommends the following language for section 5.2. The reviewer did not recommend a boxed warning.

> Glasdegib is associated with concentration-dependent QTc prolongation. Heart rate corrected QT (QTc) interval prolongation has been observed in patients treated with [glasdegib] at a supratherapeutic dose of >270 mg. In a thorough QT study in 36 healthy subjects treated with [glasdegib], at steady state therapeutic (achieved with a 150 mg single dose) plasma concentrations, the largest mean QTc interval change was 8.03 msec [see Clinical Pharmacology (12.2)]. In a randomized study (Study 1) in patients with AML and high-risk MDS treated with [glasdegib] 100 mg once daily with low-dose cytarabine, QTcF interval greater than 500 ms was reported in 6.0% of patients, however, many patients were concomitantly treated with QT interval prolonging drugs., and an exposure-adjusted analysis of Study 1 showed no imbalance between QT prolongation events for patients treated with [glasdegib] with low-dose cytarabine versus patients treated with low-dose cytarabine alone.

DRISK recommends that, should glasdegib be approved, a REMS is not needed to ensure its benefits outweigh its risks. Embryo-fetal toxicity is a known effect of the class of drugs. The other drugs in the class were approved without REMS. QTc interval prolongation can be adequately described in the labeling. As reviewed by the QT IRT review team, this concern does not rise to the level of a boxed warning. A REMS is not needed to address this risk.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of glasdegib outweigh its risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

[h] The clinical review was ongoing at the time of this review.

10 Appendices

10.1 References

[1] https://www.cancer.net/cancer-types/leukemia-acute-myeloid-aml/statistics. Accessed August 28, 2018.

[2] National Organization of Rare Disorders. https://rarediseases.org/physician-guide/acute-myeloid-leukemia-aml/. Accessed August 28, 2018

[3] Norsworthy K. Efficacy data summarized from Clinical Reviewer's presentation at the Mid-cycle Team Review Meeting, July 30, 2018, and from the FDA-edited labeling as of August 29, 201 8.

[4] ClinicalTrials.gov Identifier: NCT01546038

[5] Casey D. Clinical presentation of BLA 761097 at mid-cycle meeting, May 24, 2018, and from the FDA-edited labeling as of July 10, 2018.

[6] Fang, Li. Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review. August 14, 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/

JOYCE P WEAVER
10/01/2018

ELIZABETH E EVERHART
10/01/2018
I concur

CYNTHIA L LACIVITA
10/01/2018