CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211723Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
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	211723
PDUFA Goal Date	January 23, 2020
OSE RCM #	2019-1112, 2019-1114
Reviewer Name(s)	Brad Moriyama, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	January 16, 2020
Subject	Evaluation of Need for a REMS
Established Name	tazemetostat
Trade Name	Tazverik
Name of Applicant	Epizyme, Inc.
Therapeutic Class	methyltransferase inhibitor
Formulation(s)	200 mg tablet
Dosing Regimen	800 mg orally twice daily

Table of Contents

EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Tazverik (tazemetostat) is necessary to ensure the benefits outweigh its risks. Epizyme, Inc. submitted a New Drug Application (NDA) 211723 for tazemetostat with the proposed indication for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection. The serious risks associated with tazemetostat include secondary malignancies and embryo-fetal toxicity. The applicant did not submit a REMS or risk management plan with this application.

DRM and Oncology Center of Excellence (OCE)/Office of Oncologic Diseases (OOD) agree that a REMS is not necessary to ensure the benefits of tazemetostat outweigh its risks. The efficacy of tazemetostat was supported by Study EZH-202 Cohort 5, in which the tazemetostat group had a confirmed overall response rate of 15%. The serious risks associated with tazemetostat of secondary malignancies and embryo-fetal toxicity will be addressed in the warnings and precautions section of the label. The likely prescribers will be hematologists and oncologists who should have experience managing the serious adverse events reported with tazemetostat.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Tazverik (tazemetostat) is necessary to ensure the benefits outweigh its risks. Epizyme, Inc. submitted a NDA 211723 for tazemetostat with the proposed indication for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.[1] This application is under review in the Division of Oncology 3 (DO3). The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Tazverik (tazemetostat), a NME, is a methyltransferase inhibitor, proposed for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection. Tazemetostat inhibits the histone methyltransferase enhancer of zeste homolog 2 (EZH2).[2] Tazemetostat is supplied as a 200 mg tablet. The proposed dosing regimen is 800 mg orally twice daily.[b] Tazemetostat is not currently approved in any jurisdiction. Tazemetostat was designated as fast track designation and orphan drug designation. If approved, the indication will be approved under accelerated approval based on overall response rate (ORR) and duration of response.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for tazemetostat NDA 211723 relevant to this review:

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

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

- 06/15/2017: Orphan drug designation granted
- 11/21/2017: Fast track designation granted
- 05/23/2019: NDA 211723 submission for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection received
- 09/10/2019: 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 tazemetostat. However, the review team expressed concern that the applicant had not provided adequate justification that the observed ORR provides a meaningful advantage over available therapies
- 12/18/2019: Oncologic Drugs Advisory Committee Meeting was convened to discuss whether the demonstrated benefit of tazemetostat outweigh the risks of the drug in the proposed indication. The AC voted 11 in favor/ 0 against tazemetostat.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Epithelioid sarcoma is an uncommon type of malignant soft tissue sarcoma.[3,4,5] The estimated number of new cases of soft tissue sarcoma in the United States annually is 12,000 and less than 1% of soft tissue sarcoma are due to epithelioid sarcoma.[4,c] Patients with epithelioid sarcoma may have local recurrence and metastasis.[3] The five year survival of epithelioid sarcoma with metastatic disease is 0%.[2,4,d]

3.2 Description of Current Treatment Options

The treatment of epithelioid sarcoma with localized disease includes wide surgical excision and for advanced stage disease includes systemic chemotherapy.[3,4] While there are no specific therapies approved by the FDA for the treatment of epithelioid sarcoma, doxorubicin alone or in combination with other chemotherapy and pazopanib have been used to treat patients with epithelioid sarcoma.[2,4] Doxorubicin hydrochloride was approved by the FDA for the treatment of metastatic soft tissue sarcoma and pazopanib was approved by the FDA for the treatment of advanced soft tissue sarcoma who have received prior chemotherapy.[6,7] Doxorubicin hydrochloride was approved in 1974, labeling includes a boxed warning for cardiomyopathy, secondary malignancies, extravasation and tissue necrosis, and severe myelosuppression. The other serious risks associated with doxorubicin hydrochloride in the warnings and precautions section of the label include arrhythmias, tumor lysis syndrome, potentiation of radiation toxicity and radiation recall, and embryo-fetal toxicity. Pazopanib was approved in 2009 and labeling includes a boxed warning for the risk of hepatotoxicity. Pazopanib was initially approved

[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.*

with a Medication Guide REMS which was removed in April 2011, but was retained as part of labeling. The other serious risks associated with pazopanib in the warnings and precautions section of the label include QT prolongation and Torsades de pointes, cardiac dysfunction, hemorrhagic events, arterial thromboembolic events, venous thromboembolic events, thrombotic microangiopathy, gastrointestinal perforation and fistula, interstitial lung disease/pneumonitis, reversible posterior leukoencephalopathy syndrome, hypertension, wound healing, hypothyroidism, proteinuria, infection, increased toxicity with other cancer therapy, increase toxicity in developing organs, and embryo-fetal toxicity.

4 Benefit Assessment

The pivotal trial NCT 02601950 (Study EZH-202 Cohort 5) supporting this application for efficacy and safety consisted of a Phase 2 multicenter open-label single arm trial which evaluated tazemetostat in patients with histologically confirmed, metastatic, or locally advanced epithelioid sarcoma.[1,4] In Study EZH-202 Cohort 5, 62 patients received tazemetostat 800 mg orally twice daily. The primary endpoint was confirmed ORR. The tazemetostat group had a confirmed ORR of 15% (95% CI 7% to 26%) with a duration of response which ranged from 3.7 to more than 24.5 months. The OCE/OOD recommended accelerated approval based on the currently available data.[e]

5 Risk Assessment & Safe-Use Conditions[f]

The safety of tazemetostat was evaluated in NCT 02601950 (Study EZH-202 Cohort 5).[1,4] In the safety population from this clinical trial, 62 patients received tazemetostat. Discontinuation due to an adverse event occurred in 1/62 (1.6%) in the tazemetostat group.[8] Common adverse reactions reported with tazemetostat included pain, fatigue, nausea, decreased appetite, vomiting, and constipation.

In Study EZH-202 Cohort 5, seven deaths occurred within 30 days of the last dose in the tazemetostat group.[4] The FDA clinical reviewer concluded that the deaths were due to disease progression.

The serious risks[g] associated with tazemetostat of secondary malignancies and embryo-fetal toxicity are summarized in the section below.

5.1 SECONDARY MALIGNANCIES

Secondary malignancies have been reported with tazemetostat.[1] Secondary malignancies occurred in 6 out of 822 patients (0.7%) in clinical trials.[4] Two adult patients developed myelodysplastic syndrome, 3 adult patients developed acute myeloid leukemia, and 1 pediatric patient developed T-cell

[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.*
[f] 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.*
[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

lymphoblastic lymphoma. If approved, this risk will be communicated in the warnings and precautions section of the label.

5.2 EMBRYO-FETAL TOXICITY

Tazemetostat may cause fetal harm based on animal studies and the mechanism of action of the drug. No clinical data is available with tazemetostat in pregnancy in humans. The proposed label recommends in females of reproductive potential to verify pregnancy status before starting tazemetostat and that effective non-hormonal contraception be used during treatment and for 6 months after the last dose. In addition, in males with a female partner of reproductive potential it is recommended that effective contraception be used during treatment and for at least 3 months after the last dose. If approved, this risk will be communicated in the warnings and precautions section of the label.

6 Expected Postmarket Use

If approved, tazemetostat will primarily be used in both inpatient and outpatient settings. The likely prescribers will be hematologists and oncologists.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for tazemetostat beyond routine pharmacovigilance and labeling.

8 Discussion of Need for a REMS

The OCE/OOD recommends approval of tazemetostat on the basis of the efficacy and safety information currently available. The indication will be approved under accelerated approval based on ORR and duration of response. Tazemetostat is a methyltransferase inhibitor and if approved will be the first FDA approved treatment for metastatic or locally advanced epithelioid sarcoma not eligible for complete resection. The efficacy of tazemetostat was supported by Study EZH-202 Cohort 5, in which the tazemetostat group had a confirmed ORR of 15%. The serious risks associated with tazemetostat of secondary malignancies and embryo-fetal toxicity will be communicated in the warnings and precautions section of the label.

Epithelioid sarcoma is an uncommon type of malignant soft tissue sarcoma. The estimated number of new cases of soft tissue sarcoma in the United States annually is 12,000 and less than 1% of soft tissue sarcoma are due to epithelioid sarcoma. The five year survival of epithelioid sarcoma with metastatic disease is 0%. The likely prescribers will be hematologists and oncologists who should have experience managing the serious adverse events reported with tazemetostat. Based on the efficacy and risk associated with tazemetostat for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection, the DRM and OCE/OOD recommendation is that a REMS is not necessary to ensure that the benefits outweigh the risks.

9 Conclusion & Recommendations

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

10 Appendices

10.1 REFERENCES

[1] Proposed prescribing information for tazemetostat as currently edited by FDA, Accessed December 31, 2019 .

[2] Epizyme, Inc. Tazemetostat. Module 2.5. clinical overview. May 3, 2019.

[3] Thway K, Jones RL, Noujaim J, Fisher C. Epithelioid Sarcoma: Diagnostic Features and Genetics. Adv Anat Pathol. 2016;23(1):41-9.

[4] FDA Briefing Document for tazemetostat. Meeting of the Oncologic Drugs Advisory Committee Meeting. December 18, 2019.

[5] Asano N, Yoshida A, Ogura K, et al. Prognostic Value of Relevant Clinicopathologic Variables in Epithelioid Sarcoma: A Multi-Institutional Retrospective Study of 44 Patients. Ann Surg Oncol. 2015;22(8):2624-32.

[6] Doxorubicin hydrochloride injection package insert. New York, NY: Pfizer Labs Division of Pfizer Inc; 2019 December.

[7] Votrient (pazopanib) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2017 May.

[8] Ward A. Division of Oncology 3. NDA 211723: Tazemetostat. FDA Opening Remarks slides. Meeting of the Oncologic Drugs Advisory Committee Meeting. December 18, 2019.

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/s/

BRAD T MORIYAMA
01/16/2020 03:05:14 PM

CYNTHIA L LACIVITA on behalf of NAOMI S BOSTON
01/16/2020 09:09:06 PM

CYNTHIA L LACIVITA
01/16/2020 09:10:15 PM