CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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	212576
PDUFA Goal Date	August 11, 2020
OSE RCM #	2019-2538 and 2540
Reviewer Name	Mei-Yean Chen, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	June 15, 2020
Subject	Evaluation of Need for a REMS
Established Name	Decitabine and Cedazuridine
Trade Name	Inqovi
Name of Applicant	Astex Pharmaceuticals Inc.
Therapeutic Class	Decitabine: a nucleoside metabolic inhibitor and Cedazuridine: a cytidine deaminase inhibitor.
Formulation(s)	Fixed dose combination (FDC) tablet, one tablet contains 35 mg decitabine and 100 mg cedazuridine
Dosing Regimen	One tablet orally once daily on days 1 through 5 of each 28-day cycle

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Inqovi (decitabine and cedazuridine) is necessary to ensure the benefits outweigh its risks. Astex Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 212576 for Inqovi with the proposed indication for the treatment of adult patients with myelodysplastic syndrome (MDS) including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups. The risks associated with Inqovi include myelosuppression and embryo-fetal toxicity. The applicant did not submit a proposed REMS or risk management plan with this application.

Division of Risk Management (DRM) and Division of Hematology Malignancies 1 (DHM1) has agreed that a REMS is not needed to ensure the benefits of Inqovi outweigh its risks. Both MDS and CMML are serious diseases with substantial risk of morbidity and mortality due to cytopenia and risk of transforming to AML. The current treatment options for MDS and CMML are decitabine intravenously for 5 days or azacitabine intravenously or subcutaneously for 5 days every 28-day cycle. Inqovi is available as an oral tablet. If approved, Inqovi offers a new option that significantly reduce the burden of patients and their caregivers with the equivalent efficacy of IV decitabine.

This reviewer recommends that, if Inqovi is approved, a REMS is not necessary to ensure its benefits outweigh its risks. Myelosuppression and embryo-fetal toxicity will be communicated in Section 5 of the label, Warnings and Precautions, as well as instructions how to withhold and reduce dose in Section 2 Dosage and Administration. At the time of this review, none of these risks warrants a boxed warning. The clinicians, typically oncologists/hematologist, who will prescribe Inqovi are familiar by their experiences and trainings in the management of these toxicities.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME)[a] Inqovi (decitabine and cedazuridine) is necessary to ensure the benefits outweigh its risks. Astex Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 212576 for Inqovi (decitabine and cedazuridine) with the proposed indication for the treatment of adult patients with myelodysplastic syndrome (MDS) including previously treated and untreated, de novo and secondary MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chromic myelomonocytic leukemia [CMML]) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System (IPSS) groups. This application is under review in the Division of Hematology Malignancies 1 (DHM1). The applicant did not submit a proposed REMS or risk management plan with this application.

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

2 Background

2.1 PRODUCT INFORMATION

Inqovi is a fixed dose combination (FDC) product, which contains 35 mg of decitabine and 100 mg cedazuridine. Decitabine is a DNA hypomethylating compound. After phosphorylation, decitabine is incorporated into DNA and inhibits DNA methyltransferase causing hypomethylation and subsequent cell death. Decitabine is not orally bioavailable because of rapid clearance by cytidine deaminase (CDA) in the gut and liver. Cedazuridine, an NME, is a CDA inhibitor. Simultaneous oral administration of cedazuridine with decitabine increases systemic exposure of decitabine and allows for the oral delivery of decitabine.

The recommended dose of Inqovi is one tablet orally once daily on days 1 through 5 of each 28-day cycle for a minimum of four cycles until disease progression or unacceptable toxicity.[b] Inqovi is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 212576 relevant to this review:

- 12/18/2013: Investigation New Drug (IND) IND 116145 submission for Inqovi was received.
- 08/21/2019: Orphan drug designation granted.
- 12/11/2019: NDA 212576 submission received
- 03/19/2020: 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 Inqovi.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

MDS comprise a group of hematologic malignancies that arise from mutations in hematopoietic stem cells. For most patients, the precise cause of the mutations is unknown, but in some it is associated with exposure to cytotoxic chemotherapy and/or ionizing radiation or, rarely, after environmental toxins (e.g., benzene, tobacco). MDS is characterized by clonal hematopoiesis, abnormal cellular maturation resulting in one or more cytopenias such as anemia, neutropenia, and/or thrombocytopenia The median age at diagnosis of MDS is approximately 70 years, and prognosis is poor with median survival of 1.3 year and 0.4 year in patients with intermediate-2 and high-risk MDS, respectively. Patients with MDS are at risk for bleeding, infection, anemia, and progression to acute myeloid leukemia (AML).[c] The

[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.*

incidence of MDS that progresses to AML is about 30%. Compared to AML, patients with MDS have lower percentages of blasts in the peripheral blood and bone marrow by less than <20%.[1]

Chronic myelomonocytic leukemia (CMML) is characterized by a persistent peripheral blood monocytosis greater than 10% of white blood cells (WBCs). CMML is often accompanied by anemia and/or thrombocytopenia. The World Health Organization (WHO) currently categorizes CMML as a myelodysplastic/myeloproliferative neoplasm (MDS/MPN) syndrome. The treatment for CMML is similar to that for MDS since CMML was previously classified as MDS.[2]

MDS are diagnosed in slightly more than 10,000 people in the United States (US) per year,[3] corresponding to an age-adjusted incidence rate of 4.5 per 100,000 persons. This estimate excluded a total of 2,961 cases of CMML, which corresponds to a CMML-specific age-adjusted incidence rate of 0.5 per 100,000.[d]

The main prognostic classification system for MDS is the International Prognostic Scoring System (IPSS), which was introduced in 1997 and revised in 2012 (IPSS-Revised [IPSS-R]). The IPSS-R uses slightly different cytopenia cutoff points and incorporates the MDS cytogenetic score. IPSS-R categorizes MDS into 5 risk groups: very low, low, intermediate, high, and very high. Using IPSS-R criteria, the expected median survival for intermediate, high-risk, and very high-risk groups are 3.2, 1.4, and 0.7 years, respectively.[4]

There is no universally adopted risk classification system for CMML. The 2016 WHO classification defined 3 groups: CMML-0, CMML-1, AND CMML-2. Similar to MDS, the main manifestations are those of the underlying cytopenia, including fatigue and dyspnea due to anemia, infections, and bleeding. The median survival duration in these patients is 12 to 18 months.[5]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Because outcomes for patients with MDS are varied, individual risk stratification using tools, such as IPSS-R, is important in managing patients - including selecting candidates for allogeneic hematopoietic stem cell transplant (ASCT). ASCT is the only potentially curative therapy for MDS. Some patients with MDS have mild cytopenia and are asymptomatic at the time of diagnosis. Early treatment of MDS is not known to be beneficial in terms of preventing clonal evolution or death. Observation is appropriate for asymptomatic lower risk patients until their cytopenia worsen or they become more symptomatic.

The goals of therapy for patients with MDS are to reduce disease-associated symptoms and the risk of disease progression and death, thereby improving both quality and quantity of life. The only FDA-approved treatments for intermediate and high-risk MDS and CMML are the hypomethylating agents azacytidine (Vidaza, FDA approved in 2004) and decitabine (Dacogen, FDA approved in 2006). Lenalidomide (Revlimid) is only approved in transfusion-dependent anemia in patients with low or

[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.*

intermediate-1 risk MDS with 5q deletion. Lenalidomide is not relevant to treat patients with higher risk MDS or CMML.

Table: Summary of Treatment Options Relevant to Proposed Indication

Generic name (trade name)	Indication	Dosing/Administration	Safety Issues	Boxed Warning
Decitabine (Dacogen)[6]	MDS, CMML	3-day: 15 mg/m^2 IV* every 8 hours for 3 days 5-day: 20 mg/m^2 IV* daily for 5 days	Myelosuppression, embryo-fetal toxicity	None
Azacitabine (Vidaza)[7]	MDS, CMML	75 mg/m^2 IV* or SC** daily for 7 days *IV: intravenous **SC: subcutaneous	Myelosuppression, hepatotoxicity, renal toxicity, tumor lysis syndrome, embryo-fetal toxicity	None

4 Benefit Assessment

The efficacy of Inqovi was evaluated in the following two studies.[8]

Study ASTX727-01-B (NCT 02103478)

This was an open-label, randomized, 2-cycle, 2-sequence crossover study, which included eighty adult patients with MDS (IPSS intermediate-1, intermediate-2, or high-risk) or CMML. Eighty patients were randomized 1:1 to received Inqovi orally one tablet in cycle 1 and decitabine 20 mg/m^2 intravenously (IV) in cycle 2 or the reverse sequence. Both Inqovi and IV decitabine were given once daily on days 1 through 5 of the 28-day cycle until disease progression or unacceptable toxicity. Twelve (15%) of the 80 patients went on to stem cell transplantation after Inqovi therapy. The median age of patients were 71 years (range 32 to 90), 76 % male, 93% White, 3% Black, 1% Asian, and 4% other races.

The efficacy outcome measures were complete response (CR) and the rate of conversion from transfusion dependence to transfusion independence. The CR was 18% with 95% confidence interval (CI) of 10 and 28. The median duration of CR were 8.7 months, range 1.1 to 18.2. Among the 41 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 20 (49%) became independent of RBC and platelet transfusions during any consecutive 56-day post-baseline period.[e] Of

[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.*

the 39 patients who were independent of both RBC and platelet transfusions at baseline, 25 (64%) remained transfusion-independent during any consecutive 56-day post-baseline period.

Study ASTX727-02 (NCT03306264)

This was an open-label, randomized, 2-cycle, 2-sequence crossover study that included 133 adult patients with MDS or CMML, including all French-American-British (FAB) classification criteria and IPSS Intermediate-1, Intermediate-2, or high-risk prognostic scores. Patients were randomized 1:1 to receive Inqovi one tablet orally in Cycle 1 and decitabine 20 mg/m^2 IV in Cycle 2 or the reverse sequence. Both Inqovi and IV decitabine were administered once daily on Days 1 through 5 of the 28-day cycle. Starting with Cycle 3, all patients received Inqovi one tablet orally once daily on Days 1 through 5 of each 28-day cycle until disease progression or unacceptable toxicity. Twenty-seven(20%) of the 133 patients went on to stem cell transplantation after Inqovi therapy. The median age of patients were 71 years (range 44 to 88), 65 % male, 91% White, 3% Black, 2% Asian, and 4% other races.

The efficacy outcome measures were CR and the rate of conversion from transfusion dependence to transfusion independence. The CR was 21% with 95% CI of 15 and 29. The median duration of CR were 7.5 months, range 1.7 to 17.5. Among the 57 patients who were dependent on RBC and/or platelet transfusions at baseline, 30 (53%) became independent of RBC and platelet transfusions during any consecutive 56-day post-baseline period. Of the 76 patients who were independent of both RBC and platelet transfusions at baseline, 48 (63%) remained transfusion-independent during any consecutive 56-day post-baseline period.

5 Risk Assessment & Safe-Use Conditions

The safety of Inqovi was evaluated in a pooled safety population that includes patients enrolled in Study ASTX727-01-B and Study ASTX727-02. Among 208 patients evaluated, there were 12 deaths (6%) reported, including sepsis (n=3), septic shock(n=3), pneumonia (n=2), respiratory failure (n=2), cerebral hemorrhage (n=1), and sudden death (n=1).[2] In the IV decitabine 5-day published study, 11 patients (11%) of 99 patients treated died within 30 days of study treatment.[9] For Inqovi studies, the 6% deaths within 30 days of pooled safety data set is consistent with data from IV decitabine. The medical officer concluded that the safety profile of Inqovi was consistent with the known safety profile for IV decitabine and no new safety concerns were identified. [2]

All risks[f] associated with Inqovi listed below are currently included in the draft labeling[8] in Section 5, Warnings and Precautions.

[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.*

5.1 MYELOSUPPRESSION

Inqovi can cause fatal and serious myelosuppression. Thrombocytopenia was reported in 82% of patients, with grade ≥ 3 in 76% of patients. Neutropenia was reported in 73% of patients, with grade ≥ 3 in 71% of patients. Anemia was reported in 71% of patients, with grade ≥ 3 in 55% of patients. Febrile neutropenia was reported in 33% of patients, with grade ≥ 3 in 32% of patients. Myelosuppression is the most frequent cause of dose reduction or interruption, occurring in 36% of patients. Permanent discontinuation of Inqovi due to myelosuppression occurred in 1% of patients.

Inqovi can cause fatal and serious infection. Pneumonia was reported in 21% of patients, with grade ≥ 3 in 15% of patients. Sepsis was reported in 14% of patients, with grade ≥ 3 in 11% of patients. Fatal pneumonia occurred in 1% of patients, fatal sepsis in 1%, and fatal septic shock in 1%.

If Inqovi is approved, Warnings and Precautions of labeling will include to obtain complete blood counts (CBC) prior to initiation of Inqovi, prior to each cycle, and as clinically indicated. The Dosage and Administration section of the label will include recommendations on when to withhold and adjust the dose of Inqovi if the patient experiences hematologic toxicity, active or uncontrolled infection or increases in serum creatinine, aspartate aminotransferase or alanine aminotransferase. the. Appears this way on original

5.2 EMBRYO-FETAL TOXICITY

Inqovi can cause fetal harm when administered to a pregnant woman, based on findings from human data, animal studies, and its mechanism of action. Decitabine was teratogenic, fetotoxic, and embryotoxic at doses less than the recommended human dose in nonclinical studies in mice and rats.

The draft label states to advise pregnant women of the potential risk to a fetus and to use effective contraception during therapy and for 6 months after the last dose. The draft label also recommends to advises males with female partners of reproductive potential to use effective contraception during therapy and for 3 months after the last Inqovi dose.

6 Expected Postmarket Use

If approved, it is expected that oncologists/hematologists will be the likely health care providers to prescribe Inqovi, in both inpatient and outpatient settings.

7 Risk Management Activities Proposed by the Applicant

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

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Inqovi on the basis of the efficacy and safety information currently available. The prognosis of MDS is poor with median survival of 3.2 year, 1.4 year, and 0.7 year in patients with intermediate-2, high-risk, and very high-risk MDS, respectively. The incidence of MDS

that progresses into AML is about 30%. The median survival duration of CMML is 12-18 months. MDS and CMML are serious diseases with substantial risks of morbidity and mortality due to cytopenia and the risk of progressing to AML.

The current treatment options for MDS and CMML are decitabine IV for five consecutive days or azacytidine IV or subcutaneously for five consecutive days of each 28-day cycle. In the clinical studies, the responses of oral Inqovi were similar to IV decitabine for 5 days and the safety profile of Inqovi was consistent with the known safety profile of IV decitabine. There were no new safety concerns identified with Inqovi. If approved, Inqovi offers a fixed dose combination option that can significantly reduce the burden of patients and their caregivers.

This reviewer recommends that, if Inqovi is approved, a REMS is not necessary to ensure its benefits outweigh its risks. Myelosuppression and embryo-fetal toxicity will be communicated in the labeling Section 5 Warnings and Precautions, as well as instructions how to withhold and reduce dose in Section 2 Dosage and Administration. At the time of this review, none of these risks warrants a boxed warning. The clinicians, typically oncologists/hematologist, who will prescribe Inqovi are familiar by their experiences and trainings in the management of these toxicities.

9 Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile is favorable therefore, DRM and DHM1 agree that a REMS is not necessary for Inqovi 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.

Should DHM1 have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 References

[1] Aster, JC and Stone, RM Clinical manifestations and diagnosis of MDS, www.uptodate.com, accessed 04/24/2020

[2] Inqovi NDA 212576 Assessment Aid, accessed 05/20/2020

[3] General information about MDS, www.cancer.gov/types/myeloproliferative, accessed 04/29/2020

[4] Steensma, DP Myelodysplastic syndromes current treatment algorithm 2018, Blood Cancer Journal 8, Article number: 47 (2018)

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[6] Dacogen prescribing information Dacogen.com, accessed 05/01/2020

[7] Vidaza prescribing information Vidaza.com, accessed 05/01/2020

[8] Inqovi draft prescribing information, accessed 06/08/2020

[9] Steensma, DP et al Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndrome: The alternative dosing for outpatient treatment trial Journal of clinical oncology, volume 27, issue 23 (August 10, 2009)

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