CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218944Orig1s000

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	218944
PDUFA Goal Date	December 26, 2024
OSE RCM #	2023-7012; 2023-7376
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
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Review Completion Date	November 5, 2024
Subject	Evaluation of the need for a REMS
Established Name	revumenib
Trade Name	Revuforj
Name of Applicant	Syndax Pharmaceuticals, Inc.
Therapeutic Class	menin inhibitor
Formulation(s)	25 mg, 110 mg, 160 mg tablets
Dosing Regimen	270 mg orally twice daily for patients 40kg or greater and 160 mg/m^2 orally twice daily for patients less than 40kg

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for Revuforj (revumenib) is necessary to ensure the benefits outweigh its risks. Syndax Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 218944 for revumenib with the proposed indication for the treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) rearrangement. The serious risks associated with the use of revumenib are differentiation syndrome (DS), QTc interval prolongation and embryo-fetal toxicity. The Applicant did not submit a REMS but proposed voluntary risk management activitie (b) (4)

The Division of Risk Management (DRM) and the Division of Hematology Malignancies 1 (DHM1) have determined that a REMS is not necessary to ensure the benefits of revumenib outweigh its risks. Based on the efficacy and safety information currently available, the clinical reviewer stated that revumenib shows clinically meaningful benefit and recommends approval of revumenib for the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older. The review team concluded that the clinical benefit of revumenib in this trial was established based on complete remission (CR) plus CR with partial hematologic recovery (CRh) (CR + CRh) rate of 22% in relapsed or refractory acute leukemia patients with KMT2A translocation confirmed by local testing with median duration of 6.4 months. Even though there is no significant benefit rate of conversion to transfusion independence, short-term benefits are meaningful with 27% of patients undergoing allogeneic hematopoietic stem cell transplant.

The safety profile is similar to isocitrate dehydrogenase (IDH) inhibitors for similar indications, which do not require a REMS. The review team concluded that revumenib was well tolerated with manageable toxicities with dose interruption or dose reduction. Serious risks such as DS and QTc prolongation can be managed with dose adjustments. Safety concerns including sudden death, recurrent differentiation syndrome, and hepatotoxicity require post-marketing study requirements. If approved, labeling will be similar to IDH inhibitors such as enasidenib (Idhifa) and ivosidenib (Tibsovo), which were approved for the treatment of relapsed or refractory acute myeloid leukemia (AML) with isocitrate dehydrogenase (IDH) mutations. Management of the adverse events of revumenib will be communicated in a Boxed Warning, Warnings and Precautions, Patient Counseling Information, and the Medication Guide. We do not object to the Applicant's proposed (b) (4) outside of a REMS. The review team did not find it to necessary to require the use of this material as a risk mitigation strategy as the labeling and Medication Guide include the relevant risk information.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a REMS for Revuforj (revumenib) is necessary to ensure the benefits outweigh its risks. Syndax Pharmaceuticals, Inc. submitted a New Drug Application (NDA) 218944 for revumenib with the proposed indication for the treatment of adult and pediatric patients with relapsed or refractory (R/R) acute leukemia with a lysine methyltransferase 2A gene (KMT2A) rearrangement.[1] This application is under review in the Division of Hematology Malignancies 1 (DHM1). The applicant did not submit a REMS but proposed voluntary risk management activities that include (b) (4)

2 Background

2.1 PRODUCT INFORMATION

Revumenib is a new molecular entity (NME) NDA type 505(b)(1) pathway application.[a] It is a menin inhibitor and blocks the interaction of both wild type KMT2A and KMT2A fusion proteins with menin. The binding of KMT2A fusion proteins with menin is involved in KMT2A-rearranged (KMT2Ar) acute leukemias through activation of a leukemogenic transcriptional pathway. In nonclinical in vitro and in vivo studies, revumenib demonstrated anti-proliferative and anti-tumor activity in leukemia cells harboring KMT2A fusion proteins.[1]

Revumenib is proposed to be supplied as 25 mg, 110 mg and 160 mg tablets. The recommended dosage of revumenib is 270 mg orally twice daily for patients 40 kg or greater and 160 mg/m^2 orally twice daily for patients less than 40 kg, until disease progression or unacceptable toxicity.[b,1] Revumenib is not currently approved in any jurisdiction.[2]

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for revumenib (NDA 218944) relevant to this review:

- 05/31/2019: Investigation New Drug (IND) 142693 submission for revumenib received.
- 04/20/2020: Orphan designation granted for the treatment of acute myeloid leukemia.
- 06/24/2021: Fast Track Designation was granted for the investigation of revumenib for the treatment of adult and pediatric patients with relapsed or refractory acute leukemias harboring a KMT2Ar or the nucleophosmin 1 (NPM1) mutation.
- 11/30/2022: Breakthrough Designation was granted for the treatment of adult and pediatric patients with relapsed or refractory acute leukemia harboring a KMT2A rearrangement.
- 01/26/2024: NDA 218944 submission from (b) (4) for revumenib tablets with the proposed indication for the treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a KMT2A gene rearrangement, received.
- 04/29/2024: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant at the Post Mid-cycle meeting that based on the currently available data, there were no safety issues that require a REMS for revumenib.
- 07/18/2024: A Post Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant at the meeting that the Agency has not identified safety concerns that would require a REMS for revumenib.

[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.*

- 07/24/2024: The Applicant submitted additional PK data, which constitute a major amendment, and the review timeline is extended by 3 months.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Acute leukemia is characterized by uncontrolled expansion of immature leukocytes, either myeloid or lymphoid progenitors, leading to acute myeloid leukemia (AML) and acute lymphoid leukemia (ALL), respectively. It is a life-threatening condition with poor long-term outcomes and is rapidly fatal without treatment.[3] The estimated total number of new cases of leukemia in the United States in 2024 is 62,770 with ALL estimated at 6,550 cases and AML estimated 20,800 cases. There is an estimated 23,670 deaths due to these leukemias; 1330 with ALL and 11,220 with AML.[c,d]. The five-year survival for patients diagnosed with leukemia is approximately 67%, ALL is 72% and AML is 31.9%.[4] The KMT2A-rearranged (KMT2Ar) mutation is present in approximately 10% of all leukemias but the frequency in the pediatric population, specifically infant ALL (>70%) and AML (>35%) is much higher. Acute lymphoid leukemia is mostly predominant in the pediatric population, while the AML cases are predominated in adults.[5] Patients with relapsed KMT2Ar leukemia have a poor prognosis.[6,7] The median survival of patients with R/R KMT2Ar acute leukemia is less than 1 year, and 5-year overall survival (OS) is less than 10%.[8,9,10]

3.2 Description of Current Treatment Options

The standard of care for treatment of relapsed or refractory (R/R) acute leukemias with or without KMT2Ar is intensive cytotoxic chemotherapy followed by allogeneic hematopoietic stem cell transplantation (HSCT). The general therapeutic strategy in patients with AML has not changed substantially in more than 30 years. Currently, there is no standard treatment for managing relapse in patients with AML after HSCT.[11] 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.[12] In 2017, enasidenib (Idhifa)[13] for the treatment of IDH2-mutated R/R AML was approved and in 2018 ivosidenib (Tibsovo)[14] for the treatment of IDH1-mutated R/R AML was approved. Venetoclax-based therapies have been increasingly used for treating post-transplantation relapse of AML. Mortality during re-induction remains high even with newer regimens such as venetoclax/hypomethylating agents (HMAs), especially in patients who relapse post-transplant. In these patients, mortality rates are 23% within 60 days.[11] Options are even more limited for patients who have relapsed after transplant, or for older patients who cannot tolerate chemotherapy and have relapsed after venetoclax. Complete remission (CR) rates for patients treated with salvage chemotherapy depends on age, number of prior relapses, and refractoriness to last line of therapy. In a retrospective analysis of 222 adult patients with KMT2Ar AML, Issa et al reported CR in 66% after 1st line therapy, 34% after 2nd line therapy, and 5% after 3rd or later line of therapy.[10] There remains a high unmet medical need for relapsed or refractory KMT2Ar leukemia for which there is no approved targeted therapy.[7]

[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.*

4 Benefit Assessment

The efficacy of revumenib was evaluated in a single-arm cohort of an open-label and multicenter trial (SNDX-5613-0700, NCT04065399; AUGMENT-101) in adult and pediatric patients at least 30 days old with R/R acute leukemia with a KMT2A translocation. Since the fluorescence in situ hybridization clinical trial assay (CTA) is analytically not valid, FDA analysed the efficacy cohort, which includes patients with acute leukemia having an 11q23 translocation by local assay and baseline blasts at least 5%, treated with at least one dose of study drug at the recommended dosage, and completed the Cycle 7 Day 1 visit, or discontinued earlier, or responded earlier. The 104 study patients who met these criteria are included in the efficacy cohort.[7] Patients with an 11q23 partial tandem duplication were excluded. Eligibility required a QTcF < 450 msec at study baseline. Revumenib at a dose approximately equivalent to 160 mg in adults was given orally twice daily with a strong CYP3A4 inhibitor (e.g., voriconazole, posaconazole, itraconazole and cobicistat)[7] until disease progression, unacceptable toxicity, failure to achieve morphological leukemia-free state by 4 cycles of treatment, or hematopoietic stem cell transplantation (HSCT). Twenty-four (23%) patients underwent HSCT following revumenib treatment.

Efficacy was established on the basis of the rate of complete remission (CR) plus CR with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The median follow-up was 5.73 months (range, 0.3 to 28.9 months). The efficacy results are summarized in Table 1. On subgroup analysis, CR+CRh was achieved by 18/86 (21%) of patients with AML, 3/16 (19%) of patients with ALL, and 1/2 (50%) with mixed phenotype acute leukemia (MPAL) patients.

Table 1: Efficacy Results in Patients with Relapsed or Refractory Acute Leukemia with KMT2 translocation (Study SNDX-5613-0700)

Endpoint	Revumenib (N = 104)
CR[1]+CRh[2] n (%)	22 (21.2)
95% CI	(13.8, 30.3)[6]
Median DOCR+CRh[3] (months)	6.4[6]
95% CI	(2.7, NR)
CR n (%)	13 (12.5)
95% CI	(6.8, 20.4)[6]
Median DOCR[4] (months)	4.3[6]
95% CI	(1.0, NR)
CRh n (%)	9 (8.7)
95% CI	(4.0, 15.8)[6]
Median DOCRh[5] (months)	6.4[6]
95% CI	(1.9, NR)

CI: confidence interval; NR = not reached; DOCR = duration of CR; DOCRh = duration of CRh.
1. CR is defined as bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 × 10^9/L and platelet count ≥100 × 10^9/L.
2. CRh is defined as bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; residual neutropenia (>0.5 × 10^9/L) and thrombocytopenia (>50 × 10^9/L), but the count recovery criteria for CR are not met.
3. Duration of CR+CRh is defined as the time from first CR or CRh to the first documented relapse or death, whichever occurs first.
4. Duration of CR is defined as the time from first CR to the first documented relapse or death, whichever occurs first.
5. Duration of CRh is defined as the time from first CRh to the first documented relapse or death, whichever occurs first.
6. The 95% CI of the response rate is derived using the exact method based on binomial distribution. The median of the response duration is derived using Kaplan-Meier method.

Of the 22 patients who achieved a CR or CRh, the median time to CR or CRh was 1.9 months (range: 0.9, 5.6 months). Among the 83 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 12 (14%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 21 patients who were independent of both RBC and platelet transfusions at baseline, 10 (48%) remained transfusion independent during any 56-day post-baseline period. The clinical reviewer stated that the clinical benefit of revumenib in this trial was established based on CR + CRh rate of 22% in relapsed or refractory acute leukemia patients with KMT2A translocation confirmed by local testing with median duration of 6.4 months. However, there is no significant benefit rate of conversion to transfusion independence. The median duration of treatment was short with only 6% in the pivotal study who received revumenib more than 6 months. Short-term benefits are meaningful with 27% of patients undergoing allogeneic hematopoietic stem cell transplant.[7]

5 Risk Assessment & Safe-Use Conditions

The following section is a summary of relevant safety information to date for revumenib. The safety of revumenib was evaluated in Study SNDX-5613-0700 [AUGMENT-101] (see Section 4: Benefit Assessment). [1]

The safety profile of revumenib reflects exposure in 135 patients (104 adult and 31 pediatric patients) with relapsed or refractory acute leukemia with KMT2Ar treated with revumenib a dose approximately equivalent to 160 mg in adults orally twice daily with a strong CYP3A4 inhibitor. The median duration of exposure to revumenib was 2.3 months (range <1 to 23 months), and 3% of patients were exposed for more than 6 months.[1]

Deaths

In FDA's analysis, there were 162 deaths reported in the safety database, including 151 on SNDX-5613-0700, 1 on SNDX-5613-0705 (Phase 1, open-label, nonrandomized study), 4 on SNDX-5613-0702 (Phase 1, open-label, dose-escalation study of revumenib in combination with chemotherapy), and 6 on the expanded access protocols. There were 60 fatal treatment-emergent adverse events reported in the safety database, including 47 on SNDX-5613-0700 and 13 on the expanded access protocols. For 63% of the deaths, FDA and the Applicant agreed that the root cause was the underlying malignancy. The most common TEAE reported as fatal were Infection (5%), Respiratory failure (2%), Haemorrhage (2%), and terms related to death (2%). The review team stated that a fatal adverse reaction was observed in 7/178 (4%) of participants treated at the RP2D, including 2 (1%) deaths due to DS, which warrants a boxed warning for DS.[7]

Serious Adverse Events (SAE)

Serious adverse reactions were reported in 99 (73%) patients. The most frequent serious adverse reactions (≥5%) were infection (24%), febrile neutropenia (19%), bacterial infection (17%), differentiation syndrome (12%), hemorrhage (9%), and thrombosis (5%). Adverse reactions leading to dose interruption occurred in 42% of patients. The most common adverse reactions (≥5%) leading to dose interruption were electrocardiogram QT prolonged (12%), febrile neutropenia (7%), differentiation syndrome (6%), infection (6%), hypokalemia (5%), and nausea (5%). Adverse reactions leading to dose reduction occurred in 10% of patients who received revumenib. Adverse reactions leading to a dose

reduction (>1%) included electrocardiogram QT prolonged (5%), thrombocytopenia (2%), and neutropenia (2%). Adverse reactions leading to permanent discontinuation occurred in 12% of patients. Adverse reactions resulting in permanent discontinuation (>1%) included infection (4%) and respiratory failure (2%).[1]

The most common adverse reactions (≥20%) were hemorrhage (53%), nausea (51%), musculoskeletal pain (42%), infection (41%), febrile neutropenia (35%), bacterial infection (31%), diarrhea (30%), electrocardiogram QT prolonged (29%), differentiation syndrome (27%), transaminase increased (26%), anemia (24%), decreased appetite (24%), constipation (23%), edema (23%), viral infection (23%), fatigue (22%), and hypokalemia (21%).[1]

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

5.1 DIFFERENTIATION SYNDROME (DS):

In the clinical trial, DS occurred in 39 (29%) of 135 patients treated with revumenib at the recommended dosage for relapsed or refractory acute leukemia with a KMT2A translocation, including 32% of patients with AML, 25% of patients with MPAL, and 14% of patients with ALL. DS was Grade 3 or 4 in 13% and fatal in one patient. The median time to onset was 10 days (range 3-41 days). Some patients experienced more than 1 DS event. Treatment interruption was required for 7% of patients, and treatment was withdrawn for 1%.[1] Symptoms of DS, including those seen in patients treated with revumenib, include fever, rash, musculoskeletal pain, generalized pain, dyspnea, hypoxia, peripheral edema, pleuropericardial effusion, acute renal failure, and/or hypotension. Labeling instructs to reduce the white blood cell count (WBC) to less than 25 Gi/L prior to starting, and if DS is suspected, immediately initiate treatment with systemic corticosteroids (e.g. dexamethasone 10 mg intravenously every 12 hours in adults or dexamethasone 0.25 mg/kg/dose intravenously every 12 hours in pediatric patients weighing less than 40 kg) for a minimum of 3 days, and continue until resolution of signs and symptoms. Institute supportive measures and hemodynamic monitoring until improvement. Labeling also instructs to interrupt revumenib if severe signs and/or symptoms persist for more than 48 hours after initiation of systemic corticosteroids, or earlier if life-threatening symptoms occur such as pulmonary symptoms requiring ventilator support. Labeling also states to restart steroids promptly if DS recurs after tapering corticosteroids.[1]

Similar to isocitrate dehydrogenase (IDH) inhibitors such as enasidenib (Idhifa)[13] and ivosidenib (Tibsovo)[14], which were approved for the treatment of relapsed or refractory AML with IDH mutations, labeling will include the risk of DS as a Boxed Warning. Management of DS, including recommendations for initiating intravenous steroids and hemodynamic monitoring, will likely also be communicated in the Warnings and Precautions section of the label to increase the prominence of this information and promote mitigation of DS; a Medication Guide as part of labeling to inform patients regarding the potential risks of DS will also be included. Monitoring and dosage modifications for toxicities to address the safety issues with revumenib will likely be included in the Dosage and Administration section of the label.[1]

5.2 QTC INTERVAL PROLONGATION:

In the clinical trials, QTc interval prolongation was reported as an adverse reaction in 39 (29%) of 135 patients treated with revumenib at the recommended dosage for relapsed or refractory acute leukemia with a KMT2A translocation. QTc interval prolongation was Grade 3 in 12%. Revumenib dose reduction

was required for 5% due to QTc interval prolongation. Per QT study reviewer, there were five subjects (5%) that experienced SAEs (Preferred Terms (PT): syncope [2], death, sudden death, and electrocardiogram QT prolonged) and two were fatal (death and sudden death). One subject discontinued treatment (PT: sudden death). Seventeen subjects (18%) experienced TEAE with Grade ≥ 3 (PTs: death, sudden death, syncope [3], and electrocardiogram QT prolonged [13]). There were no ventricular arrhythmias reported. The QT study reviewer also stated that most QTc prolongation-related cardiac events are confounded by subjects' cardiac history and morbidity associated with late-stage leukemia.[15] The clinical review team has observed an increased risk of QT prolongation for revumenib in patients of Asian descent. DHM2 requested QT reviewer's input and review to see if there is any plausible explanation for this unusual finding. Per QT study reviewer, they did not identify any reasons why Asian patients had higher incidence of QTc prolongation in study SNDX-5613-0700. It is plausible that the increased incidence was by chance due to the small number of Asian patients (n = 16).[16]

Labeling instructs to correct electrolyte abnormalities, including hypokalemia and hypomagnesemia, prior to treatment with revumenib. Labeling also recommends that healthcare providers perform ECG prior to initiation of treatment with revumenib, to not initiate revumenib in patients with QTcF > 450 msec, and perform and ECG at least once a week for the first 4 weeks on treatment, (b) (4) . Labeling states that more frequent monitoring may be necessary for patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval. Concomitant use of revumenib with drugs known to prolong the QTc interval may increase the risk of QTc interval prolongation. Revumenib treatment should be interrupted if QTcF increases to greater than 480 msec and less than 500 msec, and restarted at the same dose twice daily after the QTcF interval returns to less than or equal to 480 msec. Revumenib should be interrupted if QTcF increases to greater than 500 msec or by > 60 msec from baseline, and restarted revumenib twice daily at the lower dose level after the QTcF interval returns to less than or equal to 480 msec. Revumenib should be permanently discontinued in patients with ventricular arrhythmias and in those who develop QTcF interval prolongation with signs or symptoms of life-threatening arrhythmia. The risk of QTcF interval prolongation as well as monitoring will be communicated in the Warnings and Precautions section of the label. Monitoring and dosage modifications for toxicities to address the safety issues with revumenib will be included in the Dosage and Administration section of the label.[1]

5.3 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, revumenib can cause fetal harm when administered to a pregnant woman. Animal reproduction studies have demonstrated that oral administration of revumenib to pregnant rats during the period of organogenesis caused adverse developmental outcomes, including embryo-fetal mortality, malformations, and altered fetal growth at maternal exposures approximately 0.5 times the human exposure (AUC) at the recommended dose (b) (4) . The proposed label states to advise pregnant women of the potential risk to a fetus. If approved, healthcare providers should advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with revumenib and for 4 months after the last dose.[1]

6 Expected Postmarket Use

The proposed indication is for the treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a KMT2A gene rearrangement. It is expected that oncologists/hematologists, who

are familiar with the management of chemotherapeutic toxicities such as DS, QTc interval prolongation and embryo-fetal toxicity, will be the likely health care providers to prescribe revumenib in both the inpatient and outpatient setting.

7 Risk Management Activities Proposed by the Applicant

The applicant did not submit a REMS but proposed voluntary risk management activities that includes a (b) (4)

Reviewer's Comments: *These activities voluntarily proposed by the applicant are outside of a required REMS program. We do not oppose the applicant's proposal* (b) (4)

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 revumenib, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the likely prescribing population.

Revumenib is a menin inhibitor, with the proposed indication for the treatment of adult and pediatric patients with relapsed or refractory acute leukemia with a KMT2A rearrangement. Acute leukemia is a life-threatening condition with poor long-term outcomes and is rapidly fatal without treatment. There remains a high unmet medical need for relapsed or refractory KMT2Ar leukemia for which there is no approved targeted therapy. Based on the efficacy and safety information currently available, the clinical reviewer stated that revumenib shows clinically meaningful benefit and recommends approval for the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A gene (KMT2A) translocation in adult and pediatric patients 1 year and older.[1,7]

DRM and DHM1 have determined that if approved, a REMS is not necessary to ensure the benefits of revumenib outweigh its risks. Revumenib appeared efficacious in its primary outcome of rates of CR plus CRh and secondary outcomes of the DOCR+DOCRh, and the rate of conversion from transfusion dependence to transfusion independence.[1,7] The review team concluded that the clinical benefit of revumenib in this trial was established based on CR + CRh rate of 22% in relapsed or refractory acute leukemia patients with KMT2A translocation confirmed by local testing with median duration of 6.4 months. Even though there is no significant benefit rate of conversion to transfusion independence, short-term benefits are meaningful with 27% of patients undergoing allogeneic hematopoietic stem cell transplant.[7] The most concerning adverse reactions observed with the use of revumenib are risks DS, QTc interval prolongation and embryo-fetal toxicity, which are the same as in the currently approved IDH inhibitors enasidenib**Error! Bookmark not defined.** and ivosidenib**Error! Bookmark not defined.**, which are approved for the treatment of relapsed or refractory AML with IDH mutations.

Differentiation syndrome is a result of rapid proliferation and differentiation of myeloid cells, and can develop as early as one day after starting therapy, and anytime during treatment.[1] Symptoms of DS include fever, cough, difficulty breathing, rash, low blood pressure, rapid weight gain, swelling of arms or legs, or decreased urinary output.[1] In the revumenib clinical trial, 26% (38/149) of patients with relapsed or refractory acute leukemia [35/130 patients with AML and 3/19 patients with ALL/MPAL]

treated with revumenib at the recommended dosage daily experienced DS. In the monotherapy ivosidenib clinical trial, 25% (7/28) of patients with newly diagnosed AML and 19% (34/179) of patients with relapsed or refractory AML experienced DS. The 3 deaths in ivosidenib clinical trial showed manifestations of DS, however, all of these cases have other possible causes of death (e.g. infection, underlying malignancy).[14,17] In the enasidenib clinical trial, 14% of patients treated with enasidenib experienced DS, including 7% ≥Grade 3 events. The 6 deaths in the enasidenib Phase 1 of the study showed manifestations of respiratory distress, pulmonary edema, and/or multi-organ dysfunction consistent with DS.[13,18] The clinical team leader stated that DS is clearly a risk of treatment with revumenib and the life-threatening and fatal cases necessitate a boxed warning. Because treatment with revumenib is generally outpatient, a Medication Guide is also warranted. In addition, the Applicant has voluntarily proposed (b) (4) This information is also included in the proposed labeling and Medication Guide. If revumenib is approved, similar to enasidenib and ivosidenib, labeling will include the risk of DS in a Boxed Warning and in Warnings and Precautions.

QT prolongation is another risk of treatment with revumenib that includes monitoring to mitigate serious outcomes. Of the 149 patients with relapsed or refractory acute leukemia treated with revumenib in the clinical trial, adverse reactions of QTc prolongation occurred in 19% of patients less than 18 years old, 39% of patients 18 years or older, and 53% of patients 65 years or older. Of these patients, 12% were found to have a QTcF greater than 500 msec and 23% had an increase from baseline QTcF greater than 60 msec. There was an unusual incidence of higher rates of QT prolongation seen in the Asian population. The clinical team agreed with the Applicant and Interdisciplinary Review Team for Cardiac Safety Studies (IRT) that the high incidence in Asians may be by chance, especially in the absence of biological plausibility, and that the mitigation strategies described in labeling should be sufficient to prevent serious outcomes as was demonstrated in the clinical trial.[7]

In the ivodidenib clinical trial, of the 71 patients with newly diagnosed AML treated with ivosidenib in combination with azacitidine, 14% were found to have a QTc greater than 500 msec (Grade ≥3) and 22% of patients had an increase from baseline QTc greater than 60 msec. The ivosidenib clinical trial excluded patients with a QTcF ≥470 msec or other factors that increased the risk of QT prolongation or arrhythmic events (e.g. NYHA Class III or IV congestive heart failure, hypokalemia, family history of long QT interval syndrome).[14] QTc interval prolongation is discussed in the Warnings and Precautions section of the prescribing information.

There are other oncology products that prolong the QT interval approved with a Boxed Warning and a REMS that include Vanflyta, Caprelsa, and formerly Tasigna (REMS was removed in 2013). The approved product label for Vanflyta contains a Boxed Warning for QT Prolongation, torsades de pointes, and cardiac arrest. Both Caprelsa and Tasigna product labels contain a Boxed Warning for QT Prolongation, torsades de pointes and sudden death.[19,20,21]

Vanflyta (quizartinib) was approved in July 2023 to be used in combination with standard cytarabine and anthracycline induction and cytarabine consolidation and as maintenance monotherapy following consolidation chemotherapy, for the treatment of adult patients with newly diagnosed acute myeloid leukemia (AML) that is FLT3 internal tandem duplication (ITD)-positive as detected by an FDA-approved test. Vanflyta is approved with a REMS that includes elements to assure safe use (ETASU) to address the risk of QT prolongation, torsades de pointes, and cardiac arrest.[21] Of the 1,081 patients with AML treated with quizartinib in clinical trials, torsades de pointes occurred in approximately 0.2% of patients,

cardiac arrest occurred in 0.6%, including 0.4% with a fatal outcome, and 0.1% of patients experienced ventricular fibrillation.[21] Although QT prolongation is not a new or unusual adverse event in this patient population, it was determined by the FDA that quizartinib's unique mechanism of QT prolongation necessitated measures beyond labeling to effectively educate relevant healthcare providers on the risks, recommendations to mitigate these risks, and the need to counsel patients.[22]

Caprelsa (vandetinib) was approved in April 2011 for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Caprelsa is approved with a REMS that includes ETASU to address the risk of QT prolongation, torsades de pointes, and sudden death. Based on the exposure-response relationship, the mean (90% CI) QTcF change from baseline (ΔQTcF) was 35 ms for Caprelsa. In addition, 36% of patients experienced greater than 60 ms increase in ΔQTcF and 4.3% of patients had QTcF greater than 500 ms. There were 11 cases of sudden death and 2 documented cases of Torsades de pointes (TdP) in Caprelsa's clinical studies.[23]

Tasigna (nilotinib) was approved in October 2007 for the treatment of adult and pediatric patients greater or equal to 1 year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase, adult patients with chronic phase and accelerated phase resistant to or intolerant to prior therapy that included imatinib, and in pediatric patients greater than or equal to 1 year of age resistant or intolerant to prior tyrosine-kinase inhibitor therapy.[20] The maximum mean QTcF change from baseline at steady-state was 10 msec. Increase in QTcF greater than 60 msec from baseline was observed in 4.1% of the patients and QTcF of greater than 500 msec was observed in 4 patients (less than 1%). Ten cases of sudden death were reported in the original nilotinib NDA.[24] In 2007, nilotinib was approved with a postmarketing commitment for a RiskMAP to address the risk of QT prolongation. In March 2008 the Agency informed the sponsor (b) (4) that in accordance with the FDA Amendments Act of 2007, the Sponsor should submit a REMS with a Medication Guide (MG) and communication plan to address the risk of nilotinib. In March 2010, a REMS for Tasigna was approved with a MG and CP for the risk of QT prolongation.[25] Subsequent REMS assessments for Tasigna indicated that a high percentage of the prescriber population was aware of ECG monitoring intended to identify patients at risk and enhance early detection and treatment of QT prolongation, and the REMS was released in May 2013.[26]

The risk of QTc interval prolongation as well as the need for monitoring for revumenib will be communicated in the Dosage and Administration section (specifically section 2.3) and in the Warnings and Precautions section. Because the risk of QT prolongation is similar to that of ivosidenib, approved for the treatment of relapsed or refractory AML with IDH mutations, DRM and DHM1 agreed that this risk can be adequately addressed with labeling alone. Although there are REMS approved in the oncology and hematology prescribing population, specifically quizartinib and nilotinib (REMS released in 2013), which are drugs prescribed primarily by hematologists, it is expected that the prescribing population for revumenib will be more similar to the prescribing population of enasidenib and ivosidenib, and therefore should be aware of the risks of DS and QT prolongation, and how to manage these risks in this patient population.

To better characterize the safety of revumenib, the Agency has issued seven post-marketing required (PMR) studies, which include a trial to further characterize whether long-term use of revumenib is associated with increased risk of cardiac deaths, recurrent differentiation syndrome, and hepatotoxicity, a clinical trial to evaluate revumenib and M1 pharmacokinetics (PK) in patients with severe hepatic impairment, a clinical trial to evaluate revumenib and M1 pharmacokinetics (PK) in patients with severe renal impairment, a clinical trial to evaluate the absorption, distribution, metabolism, and excretion

(ADME) of revumenib and its metabolites, and three clinical trials to assess the serious potential risk of increased drug toxicity with the effect of OATP1B1 inhibitors, multidrug and CYP3A4 substrates. The Agency has issued four post-marketing commitments (PMC), which includes a study to support the availability of an in vitro diagnostic device for identifying KMT2A translocations in patients with acute leukemias for the safe and effective use of revumenib, a study to clarify the activity of revumenib in acute leukemias with various KMT2A translocations by in vitro testing, and trials to evaluate the effect of a high-fat meal on revumenib exposure.[27,28]

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits outweigh the risks of revumenib for the treatment of relapsed or refractory acute leukemia with a KMT2A translocation in adult and pediatric patients 1 year and older. The management of the risks associated with revumenib treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

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