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	217779
PDUFA Goal Date	June 16, 2024
TTT #	2023-7412
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
Team Leader	Naomi Boston, Pharm.D.
Deputy Director	Laura Zendel, Pharm.D.
Review Completion Date	June 7, 2024
Subject	Evaluation of Need for a REMS
Established Name	Imetelstat
Trade Name	Rytelo
Name of Applicant	Geron Corp
Therapeutic Class	Telomerase inhibitor
Formulation(s)	47 mg and 188 mg single dose vials for injection
Dosing Regimen	7.1 mg/kg administered by intravenous infusion every 4 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, Rytelo (imetelstat), is necessary to ensure the benefits outweigh its risks. Geron Corp., submitted a New Drug Application (NDA) 217779 for imetelstat with the proposed indication: for the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA). This application is under review in the Division of Hematologic Malignancies 1 (DHM1). The Applicant did not submit a REMS with this application. DRM and the Division of Hematologic Malignancies I (DHM1) agree that a REMS is not needed to ensure the benefits of imetelstat outweigh its risks.

Results from Study IMerge showed the rate difference for red blood cell (RBC) transfusion independence (RBC-TI) was statistically significant for imetelstat when compared to placebo [8-week RBC-TI: 24.8% (95% CI 9.9, 36.9); 24-week RBC-TI: 24.6% (95% CI 12.6, 34.2)]. However, there were no statistically significant treatment effects observed for other secondary endpoints and patient reported outcomes (e.g., fatigue).

The Warnings and Precautions section of the proposed label includes the risks of thrombocytopenia, neutropenia, infusion-related reactions, and embryo-fetal toxicity. While DHM1 notes imetelstat has increased toxicities compared to placebo, the rates of Grade 3-4 infection and hemorrhage with imetelstat are similar to placebo suggesting that the serious consequences of cytopenias are able to be mitigated. Hematologists and oncologists who prescribe imetelstat are expected to be familiar with managing cytopenias as they characterize MDS and are associated with other products that treat MDS.

Because of uncertainties regarding the benefit-risk profile of imetelstat, the Agency held an Oncologic Drugs Advisory Committee (ODAC) meeting on March 14, 2024. The ODAC voted (yes: 12; no: 2) in favor that the benefits of imetelstat outweigh the risks. Given the ODAC's input and the high unmet need, the review team determined that the benefits outweigh the risks and recommends regular approval of imetelstat for the following indication: for the treatment of adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA). Risks and risk mitigation will be communicated to stakeholders within labeling via Dosing & Administration and Warnings & Precautions and a Medication Guide directed towards patients.

1 Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity, Rytelo (imetelstat), is necessary to ensure the benefits outweigh its risks. Geron Corp., submitted a New Drug Application (NDA) 217779 for imetelstat with the proposed indication: for the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA). This application is under review

in the Division of Hematologic Malignancies 1 (DHM1). The Applicant did not submit a REMS with this application. However, Geron Corp., submitted a "non-REMS statement," with this NDA proposing to utilize continuous routine post marketing pharmacovigilance surveillance activities, periodic re-evaluation of the imetelstat labeling and submit annual reports in order to address and identify any potential new risks that may be reported for imetelstat.[1]

2 Background

2.1 PRODUCT INFORMATION

Rytelo (imetelstat), a new molecular entity,[a] is a covalently-lipidated 13-mer oligonucleotide that acts as a competitive inhibitor of the enzyme telomerase for which shorter telomere length and high telomerase activity have been reported as poor prognostic features in lower-risk MDS.[2] Imetelstat is proposed for the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA).[3] Imetelstat is proposed to be supplied as lyophilized powder for injection as a 47 mg vial (equivalent to 50 mg of imetelstat sodium) and a 188 mg vial (equivalent to 200 mg of imetelstat sodium).

The FDA-approved indication will be: for the treatment of adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA).[4]

The recommended dosage of imetelstat is 7.1 mg/kg administered as an intravenous infusion over 2 hours every 4 weeks. Treatment is continued as long as the patient continues to benefit and does not experience unacceptable toxicity.[b]

Imetelstat is not approved in any other jurisdiction.

2.2 REGULATORY HISTORY

- **04/08/2005:** IND 072072 for imetelstat was submitted, intended for use in patients with advanced hematological and solid tumor malignancies.
- **12/23/2015**: Imetelstat was granted an orphan drug designation (ODD) for or the treatment of patients with MDS.
- **10/27/2017**: Imetelstat was granted fast track designation for the treatment of adult patients with transfusion-dependent anemia due to low or intermediate-1 risk MDS that is not associated with the del5q abnormality and who are refractory or resistant to treatment with an ESA.
- **06/16/2023**: NDA 217779 was submitted for imetelstat for the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk myelodysplastic syndromes

[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.*

(MDS) who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA).

- **11/15/2023:** A Post Mid-Cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that there is currently no need for a Risk Evaluation and Mitigation Strategy (REMS) for imetelstat.
- **03/14/2024**: The Oncologic Drugs Advisory Committee (ODAC) Meeting was convened to discuss imetelstat. The ODAC voted 12/2 in favor that the benefits of imetelstat outweigh its risks. A REMS proposal was not discussed.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders resulting from the clonal expansion of a hematopoietic progenitor, causing bone marrow dysplasia, ineffective hematopoiesis, and risk of transformation to acute myeloid leukemia (AML).[2] The annual incidence of MDS is approximately 4 per 100,000 people, according to the United States Surveillance, Epidemiology, and End Results database.[c] The median age at presentation is 70 years. MDS is more common in males, except for MDS with del(5q), which is more common in females.[5]

Newly diagnosed patients are stratified into risk categories based on blast percentage, number of cytopenias, and cytogenetic profile. For lower-risk MDS,[d] median survival has been reported to range from 2 to > 10 years, depending on a number of clinical factors. Most patients with lower-risk MDS are affected by anemia and anemia-related symptoms, which may negatively impact health-related quality of life.[e] Anemia and transfusion dependence have also been reported to correlate with shorter survival in patients with MDS.[2]

3.2 Description of Current Treatment Options

For transfusion-dependent anemia in lower-risk MDS, erythropoiesis stimulating agents (ESA) have been considered first-line therapy, although their use is off-label. Reblozyl (luspatercept-aamt), an erythroid maturation agent, was approved in August of 2023, for the treatment of anemia without previous erythropoiesis stimulating agent use (ESA-naïve) in adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS) who may require regular red blood cell (RBC) transfusions.[6] Lenalidomide is also FDA-approved for transfusion-dependent anemia in IPSS low- or intermediate-1 risk MDS, however its use is limited to those with deletion 5q (del5q). Of importance, lenalidomide is only available through the Lenalidomide REMS (restricted distribution) due to the risk of embryo-fetal

[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] Lower-risk MDS: conventionally defined as MDS with a risk score in the low or intermediate-1 range for International Prognosis Scoring System (IPSS), or in the very low, low, or intermediate range for Revised International Prognosis Scoring System (IPSS-R)
[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.*

toxicity. It was also approved with a Boxed Warning that includes embryo-fetal toxicity, hematologic toxicity, and venous and arterial thromboembolism.[7] Other agents that are broadly approved for MDS including chronic myelomonocytic leukemia (CMML) are azacytidine, decitabine, and decitabine-cedazuridine. These antineoplastic agents are DNA methylation inhibitors that are frequently reserved for higher-risk MDS or refractory lower-risk-MDS in clinical practice.[2]

4 Benefit Assessment

The efficacy of imetelstat was evaluated in Study MDS3001-Part 2, a phase 3, randomized, double-blind, placebo-controlled, multicenter trial (IMerge; NCT02598661) in 178 patients enrolled with International Prognostic Scoring System (IPSS) low- or intermediate-1 risk MDS who were transfusion-dependent requiring ≥ 4 red blood cell (RBC) units over an 8-week period during the 16 weeks prior to randomization.[4] Eligible patients were required to have failed to respond, have lost response, or be ineligible for ESAs; and have an absolute neutrophil count of 1.5 x 10^9/L or greater and platelets 75 x 10^9/L or greater. Patients with del(5q) cytogenetic abnormality or had received prior treatment with lenalidomide or hypomethylating agents were ineligible.[4]

Patients were randomized in a 2:1 ratio to receive imetelstat (n = 118) or placebo (n = 60). The dosage regimen was imetelstat 7.1 mg/kg administered as an intravenous infusion in 28-day treatment cycles until disease progression or unacceptable toxicity. The primary endpoint was the proportion of patients who achieved ≥ 8 week RBC transfusion independence (TI), defined as the absence of RBC transfusion(s) during any consecutive 8 weeks (56 days) period, and during any consecutive 24 weeks (168 days) period, respectively, from randomization until the start of subsequent anti-cancer therapy (if any).[4,f] The key secondary endpoint was ≥ 24-week RBC-TI. Other secondary endpoints included hematologic improvement-erythroid (HI-E) per international working group (IWG) 2006 criteria, complete remission/partial remission (CR/PR), and overall survival (OS).[8] Additionally, exploratory analyses were performed to investigate the impact of imetelstat on patient reported outcomes (PROs) concepts of interest (COIs) that were identified as relevant for patients with lower-risk MDS: fatigue, physical function, dyspnea, pain, bruising, and systemic symptoms.[8]

Results showed the following:[8]

- For the primary endpoint, 8-week RBC-TI, the rate difference was 24.8% (95% CI 9.9, 36.9).
- For the key secondary endpoint, 24-week RBC-TI, the rate difference was 24.6% (95% CI 12.6, 34.2).
- The median duration of response was 51.6 weeks (95% CI 26.9, 83.9) for 8-week RBC-TI responders, suggesting a clinically meaningful duration of benefit for this subset of patients. However, the median duration of response was only 5.0 weeks (95% CI 4.0, 7.7) when considering all patients treated with imetelstat.

The review team concluded imetelstat demonstrated superiority over placebo in Study MDS3001-Part 2 (Phase 3) on the primary endpoint of 8-week RBC-TI and the key secondary endpoint of 24-week RBC-TI.[8] The rate difference in these endpoints were statistically significant. A subset of patients, the 8-week

[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.*

RBC-TI responders, had a clinically meaningful duration of RBC-TI benefit. However, the HI-E, CR/PR, and OS results showed no major difference between treatment arms and are not supportive of a disease-modifying treatment effect. And while the patient-reported outcomes were exploratory, they were not supportive of a treatment effect as there was no major difference between treatment arms regarding the patient reported outcome of interest, deterioration of fatigue.[8]

5 Risk Assessment & Safe-Use Conditions

The safety of imetelstat was evaluated in Study IMerge, described above. The most common (≥ 10% with a difference between arms of > 5% compared to placebo) adverse reactions, including laboratory abnormalities, were decreased platelets, decreased white blood cells, decreased neutrophils, increased aspartate aminotransferase (AST), increased alkaline phosphatase, increased alanine aminotransferase (ALT), fatigue, prolonged partial thromboplastin time, arthralgia/myalgia, COVID-19 infections, and headache.[4]

Table 1:[4] Select Laboratory Abnormalities (> 10%) That Worsened from Baseline in Patients with Disease Who Received imetelstat with a Difference Between Arms of > 2% Compared to Placebo in Study IMerge

Laboratory Abnormality	Imetelstat[1]		Placebo[2]	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Platelet count decreased	97	65	34	8
White blood cell count decreased	94	53	59	1.7
Neutrophil count decreased	92	72	47	7
PTT prolonged	26	1	18	4
Chemistry				
AST increased	53	0.8	22	1.7
ALP increased	48	0	12	0
ALT increased	43	3.4	37	5

Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.
ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; PT = prothrombin time; PTT = partial thromboplastin time
[1] The denominator used to calculate the rate varied from (b) (4) to 118 based on the number of patients with a baseline value and at least one post-treatment value. [2] The denominator used to calculate the rate varied from (b) (4) to 59 based on the number of patients with a baseline value and at least one post-treatment value.

Serious adverse reactions occurred in 32% of patients who received imetelstat. Serious adverse reactions in > 2% of patients included sepsis (4.2%) and fracture (3.4%).[g] Fatal adverse reactions occurred in 0.8% of patients who received imetelstat, including sepsis (0.8%). Clinically relevant adverse reactions in < 5% of patients who received imetelstat included febrile neutropenia, sepsis, gastrointestinal hemorrhage , and hypertension. The Warnings and Precautions section of the proposed

[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.*

imetelstat label includes the risks of thrombocytopenia, neutropenia, infusion-related reactions (IRR), and embryo-fetal toxicity. In embryo-fetal development toxicity studies, imetelstat was not teratogenic, however labeling will include recommendations for contraception due to risk of miscarriage. Symptoms associated with IRR were seen in 8% of patients who received imetelstat. Labeling will include recommendations for pre-medications and rate changes to mitigate this risk.

The FDA review team concluded imetelstat is associated with a substantial risk of neutropenia and thrombocytopenia requiring intervention such as myeloid growth factors and/or platelet transfusions. There were additional safety signals for hepatic toxicity, fracture, headache, arthralgia/myalgia, pruritus, and bone pain. However, the rates of Grade 3-4 infection and hemorrhage with imetelstat are similar to placebo, suggesting that serious consequences of cytopenias are able to be mitigated. Per the Oncology Drug Advisory Committee discussion on March 14, 2024, the safety profile of imetelstat is acceptable for patients with transfusion-dependent anemia due to LR-MDS.[8]

5.1 THROMBOCYTOPENIA

Grade 3 or 4 decreased platelets occurred in 65% of patients treated with imetelstat. The median time to onset of the first occurrences was 6 weeks (range: 2 to 88 weeks). Grade 3 or 4 bleeding was seen in 2.5% of patients, including gastrointestinal bleeding (1.7%) and hematuria (0.8%). The Warnings and Precautions section of the proposed imetelstat label addresses this risk by stating to monitor patients with thrombocytopenia for bleeding. It also states to monitor complete blood cell counts prior to initiation of imetelstat, weekly for the first two cycles, prior to each cycle thereafter, and as clinically indicated. Healthcare providers are instructed to administer platelet transfusions as appropriate. The labeling also includes recommendations to delay the next cycle and resume at the same or reduced dose, or permanently discontinue treatment if severe thrombocytopenia recurs.[4]

5.2 NEUTROPENIA

New or worsening Grade 3 or 4 decreased neutrophils occurred in 72% of patients with MDS treated with imetelstat. The median time to onset was 4.6 weeks (range: 1 to 81 weeks). Febrile neutropenia occurred in 0.8% and sepsis in 4.2%. The Warnings and Precautions section of the proposed imetelstat label addresses this risk by stating to monitor patients with Grade 3 or 4 neutropenia for infections, including sepsis. It also states to monitor complete blood cell counts prior to initiation of imetelstat, weekly for the first two cycles, prior to each cycle thereafter, and as clinically indicated. Healthcare providers may administer growth factors and anti-infective therapies for treatment or prophylaxis as appropriate. The labeling also includes recommendations to delay the next cycle and resume at the same or reduced dose, or permanently discontinue treatment if severe neutropenia recurs.[4]

6 Expected Postmarket Use

If approved, imetelstat will be primarily prescribed in the inpatient and outpatient setting (e.g., infusion center) by hematologists and oncologists who treat MDS. The prescribers of imetelstat are expected to be familiar with managing adverse events including cytopenias as they characterize MDS and are associated with many of the drugs that treat MDS. Additionally, infusion-related reactions are expected to be manageable in the healthcare settings in which imetelstat will be used. Lastly, MDS occurs more

frequently in an older patient population (median 70 years old at presentation), therefore this patient population may be at lower risk for pregnancy exposure while taking imetelstat. Imetelstat is not teratogenic and will not be contraindicated in pregnancy.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not submit a REMS with this application. However, Geron Corp., submitted a "non-REMS statement," with this NDA proposing to utilize continuous routine post marketing pharmacovigilance surveillance activities, periodic re-evaluation of the imetelstat labeling and submit annual reports in order to address and identify any potential new risks that may be reported for imetelstat.

8 Discussion of Need for a REMS

Patients with lower-risk MDS are often affected by anemia and anemia-related symptoms, which may negatively impact health-related quality of life. Anemia and transfusion dependence have also been reported to correlate with shorter survival in patients with MDS. Median survival has been reported to range from 2 to > 10 years in this patient population.

The FDA review team determined that Study MDS3001-Part 2 (Phase 3), met its primary endpoint of 8-week RBC-TI in addition to the key secondary endpoint of 24-week RBC-TI. The rate difference of imetelstat compared to placebo for these endpoints were statistically significant. However, there was no evidence of a statistically significant treatment effect on the key secondary endpoint, other secondary endpoints reflective of a disease-modifying effect, or on PROs (e.g., improvement in fatigue or other anemia-related symptoms).

The safety concerns for imetelstat include the high rate of cytopenias including grade 3-4 neutropenia and thrombocytopenia. Because of the uncertainties regarding the benefit-risk profile of imetelstat, the Agency held an Oncologic Drugs Advisory Committee (ODAC) Meeting on March 14, 2024. The ODAC voted (yes: 12; no: 2) in favor that the benefits of imetelstat outweigh the risks. Collectively, the Committee members agreed that Study MDS3001 met the primary endpoint. Committee members also acknowledged the cytopenias seen in the trial, however, most expressed that these toxicities can be well controlled in a real-world setting as the intended population is closely monitored by specialists who are familiar with managing neutropenia and thrombocytopenia. Given the input from the ODAC, in addition to the high unmet need for the proposed patient population, the review team concluded that the benefits of imetelstat outweigh the risks for the treatment of adult patients with low- to intermediate-1 risk MDS with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for ESA.[8]

If approved, imetelstat will support a high unmet clinical need. Proposed labeling includes thrombocytopenia, neutropenia, infusion-related reactions, and embryo-fetal toxicity under Warnings and Precautions. Hematologists and oncologists who prescribe imetelstat are expected to be familiar with managing cytopenias as they characterize MDS and are associated with many of the drugs that treat MDS. Additionally, risks and risk mitigation related to infusion-related reactions and embryo-fetal

toxicity can be communicated to healthcare providers in labeling. Further, a Medication Guide will be included in labeling to inform patients of the risks and when to seek medical attention.

Based on the available data, DRM recommends that, should imetelstat be approved, a REMS is not necessary to ensure its benefits outweigh its risks.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary for imetelstat to ensure the benefits outweigh the risks. Taking into consideration the recommendations from the ODAC and the high unmet need for the proposed patient population, the review team concluded that the benefits of imetelstat outweigh the risks and the safety profile is acceptable for patients with transfusion-dependent anemia due to lower-risk MDS. 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

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8. Food and Drug Administration. Division of Hematologic Malignancies I. Rytelo (imetelstat). NDA 217779. Multidisciplinary Review and Evaluation. June 6, 2024.

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