

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

217779Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	June 4, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 217779
Product Name, Dosage Form, and Strength:	Rytelo (imetelstat) for Injection, 47 mg/vial and 188 mg/vial
Applicant Name:	Geron Corporation
FDA Received Date:	June 3, 2024
TTT ID #:	2023-5408-3
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Geron Corporation submitted revised carton labeling received on June 3, 2024 for Rytelo. We reviewed the revised carton labeling for Rytelo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Geron Corporation implemented all of our recommendations and we have no additional recommendations at this time.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

^a Kundreskas, J. Label and Labeling Review for Rytelo (NDA 217779). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAY 29. TTT ID: 2023-5408-2.

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/s/

JODY K KUNDRESKAS
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06/04/2024 12:24:43 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 29, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 217779
Product Name, Dosage Form, and Strength:	Rytelo (imetelstat) for Injection, 47 mg/vial and 188 mg/vial
Applicant Name:	Geron Corporation
FDA Received Date:	May 23, 2024
TTT ID #:	2023-5408-2
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Geron Corporation submitted revised container labels and carton labeling received on May 23, 2024 for Rytelo. We reviewed the revised container labels and carton labeling for Rytelo (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

Geron Corporation implemented all of our recommendations. However, we note that the route of administration lacks prominence on the carton labeling, and we provide a recommendation, below.

3 RECOMMENDATIONS FOR GERON CORPORATION

A. Carton Labeling

1. The route of administration statement lacks prominence. The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the Principal Display Panel (PDP). We recommend increasing the prominence of the route of administration by relocating this statement so that it is underneath the strength statement on the PDP. Additionally, relocate the Medication Guide statement so that it is above the package type term "Single-Dose Vial.". See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022).

^a Kundreskas, J. Label and Labeling Review for Rytelo (NDA 217779). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAY 17. TTT ID: 2023-5408-1.

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JODY K KUNDRESKAS
05/29/2024 12:00:53 PM

NICOLE F IVERSON
05/29/2024 01:46:27 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	May 17, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 217779
Product Name, Dosage Form, and Strength:	Rytelo (imetelstat) for Injection, 47 mg/vial and 188 mg/vial
Applicant Name:	Geron Corporation
FDA Received Date:	May 2, 2024 and May 13, 2024
TTT ID #:	2023-5408-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Nicole Iverson, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

Geron Corporation submitted revised container labels and carton labeling received on May 2, 2024 for Rytelo. We reviewed the revised container labels and carton labeling for Rytelo (Appendix A) and noted that the submitted revised carton labeling for the 188 mg strength was not suitable for our review due to [REDACTED] (b) (4) displayed across the Principal Display Panel (PDP), which obstructed the view. We sent an Information Request (IR) via email to Geron on May 10, 2024, requesting a clean copy of the revised draft carton labeling for our review. A clean copy of the revised 188 mg strength carton labeling was provided on May 13, 2024. We reviewed the revised container labels and carton labeling to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

We note that Geron Corporation added a Medication Guide statement to the Principal Display Panel (PDP) of the carton labeling as requested, however the statement did not include information on how the Medication Guide is provided (i.e., accompanied, enclosed, or provided separately). Additionally, we find that the route of administration and the preparation technique can be consolidated to reduce clutter on the PDP. We provide our recommendations to address these issues below. Geron implemented all of our other previous recommendations, and we have no additional recommendations at this time.

3 RECOMMENDATIONS FOR GERON CORPORATION

A. General Comment

1. The statements [REDACTED] (b) (4) can be consolidated to reduce clutter on the Principal Display Panels (PDP). Revise to “For intravenous infusion after reconstitution and dilution”.

B. Carton Labeling

1. We note the carton labeling includes the Medication Guide (MG) statement “Dispense Medication Guide to each patient.” However, the carton labeling does not include how the MG is provided (e.g., accompanied, enclosed, or provided separately). Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed, and shall state how the Medication Guide is provided. These statements shall appear

^a Kundreskas, J. Label and Labeling Review for Rytelo (NDA 217779). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAR 29. TTT ID: 2023-5408.

on the label in a prominent and conspicuous manner. Ensure the Medication Guide statement appears in accordance with 21 CFR 208.24(d).

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JODY K KUNDRESKAS
05/17/2024 07:23:34 AM

NICOLE F IVERSON
05/17/2024 09:08:55 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 17, 2024

To: Saumya Nathan, Senior Regulatory Project Manager,
Division of Hematologic Malignancies 1 (DHM1)

From: Valerie Guerrier, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: Samia Alam, Regulatory Review Officer, OPDP
Jina Kwak, Team Leader, OPDP

Subject: OPDP Labeling Comments for RYTELO (imetelstat) for injection, for intravenous use

NDA: 217779

Background:

In response to DHM1's consult request dated June 26, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide, and carton and container labeling for the original NDA submission for RYTELO (imetelstat) for injection, for intravenous use.

PI/Medication Guide:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on May 9, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on May 16, 2024.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on May 9, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Valerie Guerrier at (240) 402-2162 or Valerie.Guerrier@fda.hhs.gov.

Section	Statement from Draft	Comment
<p>HIGHLIGHTS, ADVERSE REACTIONS</p> <p>ADVERSE REACTIONS</p>	<p>The most common ($\geq 10\%$ with a difference between arms of $>5\%$ compared to placebo) adverse reactions, including laboratory abnormalities, were decreased neutrophils, decreased platelets, increased AST, increased alkaline phosphatase, increased ALT, prolonged partial thromboplastin time, COVID-19, (b) (4) decreased white blood cells, arthralgia/myalgia, headache, and fatigue.</p>	<p>OPDP notes (b) (4) is not listed in Table 5 of the ADVERSE REACTIONS section. For consistency with Tables 5 and 6, OPDP recommends removing (b) (4) and presenting the most common adverse reactions, including laboratory abnormalities, in descending order of frequency.</p>

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VALERIE GUERRIER
05/17/2024 09:38:27 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 16, 2024

To: Saumya Nathan, MSc, MS
Senior Regulatory Health Project Manager
Division of Hematologic Malignancies I (DHM1)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Laurie Buonaccorsi, PharmD
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Valerie Guerrier, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): RYTELO (imetelstat) for injection

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: NDA 217779

Applicant: Geron Corporation

1 INTRODUCTION

On June 16, 2023, Geron Corporation submitted for the Agency's review an original New Drug Application (NDA) 217779 for RYTELO (imetelstat) for injection. With this submission, the Applicant proposes and 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 collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies I (DHM1) on June 26, 2023 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for RYTELO (imetelstat) for injection.

On April 19, 2024, DHM1 requested that the Applicant revise the PPI to a Medication Guide (MG) due to risk of cytopenias (thrombocytopenia and neutropenia), of which patients should be made aware. On May 2, 2024, the Applicant resubmitted the proposed patient labeling as a MG.

2 MATERIAL REVIEWED

- Draft RYTELO (imetelstat) for injection MG received on May 2, 2024, and received by DMPP and OPDP on May 10, 2024.
- Draft RYTELO (imetelstat) for injection Prescribing Information (PI) received on June 26, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 10, 2024.
- Approved REBLOZYL (luspatercept-aamt) for injection and REVLIMID (lenalidomide) capsules comparator labeling dated August 28, 2023, and March 24, 2023, respectively.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	January 19, 2024
Requesting Office or Division:	Division of Hematologic Malignancies 1 (DHM 1)
Application Type and Number:	NDA 217779
Product Name, Dosage Form, and Strength:	Rytelo (imetelstat) for Injection, 47 mg/vial and 188 mg/vial
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Geron Corporation
FDA Received Date:	June 16, 2023 and September 18, 2023
TTT ID #:	2023-5408
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader (Acting):	Nicole Iverson, PharmD, BCPS

1 REASON FOR REVIEW

As part of the approval process for Rytelo (imeteostat) for Injection, we reviewed the proposed Rytelo Prescribing Information (PI), Patient Information, container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed Prescribing Information (PI), Patient Information, carton labeling, and container labels for Rytelo for Injection to identify deficiencies that may lead to medication errors and areas of improvement.

We identified areas of the proposed PI, carton labeling, and container labels that could be revised to improve clarity, readability, and availability of important information. For the Division we recommend ensuring each dosage referenced contains a unit of measure, clarifying how premedications are administered, removing trailing zeros, adjusting preparation and storage instructions for clarity, and aligning with the Guidance for Industry regarding products containing salt drug substances. For the Applicant, we provide recommendations for edits to the labels and labeling to ensure the readability, availability, and prominence of important information in Section 4.2.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the Patient Information is acceptable from a medication error standpoint. The proposed PI, carton labeling, and container labels for Rytelo for Injection may be improved to promote the safe use of the product. We provide specific recommendations for the Division in Section 4.1 and the Applicant in Section 4.2.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 1 (DHM 1)

A. Prescribing Information

1. General Comments

- a. As currently presented, the proprietary name is denoted by the placeholder "TRADENAME". We reference our May 3, 2023 Proprietary Name Request Conditionally Acceptable letter informing you that the proprietary name, Rytelo, was found conditionally acceptable. We recommended replacing the placeholder "TRADENAME" with the conditionally acceptable proprietary name, Rytelo.

2. Full Prescribing Information

a. Dosage and Administration Section

- i. As currently presented in section 2.2 *Premedication Instructions*, the timeframe to administer premedications prior to the infusion is unclear. Failure to provide clear instructions related to administration of required concomitant treatments may result in healthcare providers administering these medications differently than intended. We recommend clarifying the exact timeframe for administering premedications (e.g., "...30 minutes to 60 minutes prior to...").
- ii. The unit of measurement (e.g., mg) is missing after some expressions of dose in section 2.2 *Premedication Instructions*. This may lead to confusion and potential risk of wrong dose error. We recommend ensuring the unit of measure follows each numeric value of dose by revising "(25 to 50 mg)" and "(100 to 200 mg)" to "(25 mg to 50 mg)" and "(100 mg to 200 mg)", respectively.
- iii. As currently presented in section 2.2 *Premedication Instructions*, the route of administration for the premedications is not specified. Failure to provide the route of administration may result in product administration errors. We recommend revising this section to include the non-abbreviated route(s) of administration for the premedications.
- iv. Laboratory values are presented with a trailing zero throughout section 2.3 *Dose Modifications for Adverse Reactions*, which can lead to tenfold misinterpretations when the decimal point is overlooked (e.g., $1.0 \times 10^9/L$ is read as $10 \times 10^9/L$). Revise this laboratory value to remove the trailing zeros (e.g., $1 \times 10^9/L$).
- v. The instruction to prepare parenteral products aseptically is missing. Failure to include this instruction could result in deteriorated drug medication errors. Add the instruction "Use aseptic technique to prepare TRADENAME." as the second sentence in section 2.4, *Preparation and Administration*.

- vi. Table 4: Reconstitution Volumes in section 2.4 *Preparation and Administration* presents a deliverable volume with a trailing zero, which can lead to tenfold misinterpretations when the decimal point is overlooked (e.g., 6.0 mL is read as 60 mL). Revise the deliverable volume to remove the trailing zero (e.g., 6 mL).
- vii. The reconstitution instructions can be improved to enhance readability to ensure important information is not overlooked.
 - a. We recommend revising the first bullet for added clarity to, "Calculate the dose of TRADENAME needed based on the patient's body weight (kg)."
 - b. We recommend revising the second bullet to clarify that multiple vials may be required. Revise to "Determine the number of TRADENAME vials needed to achieve the dose per Table 4. More than one vial may be needed to achieve a full dose."
 - c. We recommend revising the third bullet to add the unit of measure after each expression of time and to remove (b) (4) [REDACTED] may contribute to confusion and wrong technique in product usage process. Revise to "Remove the TRADENAME vials from the refrigerator and allow the vials to sit for 10 minutes to 15 minutes (not to exceed 30 minutes) at room temperature at 20°C to 25°C (68°F to 77°F) before use."
 - d. We recommend revising the fourth bullet to improve readability. Revise to "Reconstitute each vial of TRADENAME with the volume of 0.9% Sodium Chloride Injection provided in Error! Reference source not found. directly onto the lyophilized powder to obtain a concentration of 31.4 mg/mL of imetelstat."
 - i. We recommend relocating Table 4 from the beginning of this section to underneath this bulleted instruction for continuity of reference information.
 - e. We recommend removal of the hyphen in "essentially-free".
- viii. The dilution instructions lack clarity and can be improved to enhance readability to ensure important information is not overlooked.
 - a. We recommend adding a bullet in the first position as follows: "Calculate the required volume of the

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reconstituted TRADENAME solution needed to obtain the appropriate dose according to the patient's body weight."

- b. We recommend revising the bullet that begins "From a 500 mL infusion bag..." to "Withdraw a volume equal to the required reconstituted TRADENAME solution from a 500 mL infusion bag of 0.9% Sodium Chloride Injection and discard it."
 - c. Relocate the statement "Discard any unused portion of the reconstituted solution remaining in each vial." from its current location to the end of the bullet that begins with "Add the required volume...".
- ix. The readability of information on post-reconstitution storage can be improved. Including clear information on post-reconstitution storage will inform healthcare providers during product preparation and minimize the risk of administering deteriorated drug products.
- a. We recommend adding the header "Diluted TRADENAME Solution Storage:" above the storage of diluted solution information in section 2.4 *Preparation and Administration*.
 - b. We recommend revising both instances of "...completion of intravenous infusion..." and "...hours from the time reconstitution." to "...completion of the intravenous infusion..." and "...hours from the time of reconstitution.", respectively, to improve readability.

- x. ^{(b) (4)} under Administration in section 2.4, ^{(b) (4)}

We recommend removal of this statement.

b. How Supplied/Storage and Handling Section

- i. The How Supplied section is visibly cluttered and contains unnecessary and duplicative information, which may contribute to readability issues and overlooking important information. Specifically, we recommend removing the unnecessary ^{(b) (4)}  consolidating the number of times ^{(b) (4)}  and relocating the preservative-free statement from the Storage section to the How Supplied section. We recommend revising to:

TRADENAME (imeteostat) for injection is a preservative-free, white to off-white or slightly yellow lyophilized powder, available as:

Carton Contents	NDC
One 47 mg single-dose vial	82959-112-01
One 188 mg single-dose vial	82959-111-01

- ii. As currently presented, the statement regarding preservatives is located in the storage section, where it may be overlooked. We recommend relocating the statement “ (b) (4) .” from the Storage section to How Supplied section, as shown in b(i), above.

4.2 RECOMMENDATIONS FOR GERON CORPORATION

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. The placement of (b) (4) competes with the legibility of the proprietary name, which may lead to misinterpretation of the proprietary name. (b) (4)
(b) (4)
Delete, move, or decrease the prominence (b) (4)
2. As currently presented, the established name is presented (b) (4) that lacks prominence and legibility on the principal display panel (PDP). The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent and legible information on the PDP. We recommend revising the font type, size, color, or use other means to achieve increased prominence and legibility of the established name.
3. The 188 mg strength is not clearly differentiated due to the similarity between the blue boxing color around the strength (b) (4) (b) (4) Lack of adequate differentiation may contribute to wrong strength errors. We recommend revising the color scheme of the 188 mg strength such that the each of the strengths (b) (4) appear in their own unique colors that do not overlap.
4. The discard statement “Discard unused portion” is not present next to the package type term “Single-dose vial”. Inclusion of this statement helps minimize the risk of the entire contents of the vial being given as a single dose. We recommend revising the statement “Single-Dose Vial” to “Single-Dose Vial. Discard Unused Portion.”.

5. The PDP contains unnecessary information. [REDACTED] (b) (4)

B. Container Labels

1. The “Rx Only” statement appears more prominent than other critical information such as the established name on the PDP. The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. We recommend decreasing the prominence by debolding and/or decreasing the size of the “Rx Only” statement on the PDP.
2. As currently presented, the statements [REDACTED] (b) (4) compete for prominence with other important information on the label such as proprietary name, established name, and strength. We recommend reducing the font size of these statements so that this information does not compete for prominence with the proprietary name, established name, and strength.
3. As currently presented, the bolded statements “Single-Dose Vial”, “Dosage [REDACTED] (b) (4) and “Mfd. By:” compete for prominence with other important information on the label. The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. We recommend debolding these statements so that this information does not compete for prominence with other important information.
4. As currently presented, important storage conditions may be overlooked. The storage condition “Refrigerate” should be bolded so that this important information is not overlooked which could lead to deteriorated drug medication errors. We recommend revising to: “Storage: Refrigerate at 2°C to 8°C (36°F to 46°F).”.
5. The terminology within the recommended dosage statement is inconsistent with the terminology in the Prescribing Information. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the “Dosage [REDACTED] (b) (4): See prescribing information.” statement to “Dosage: See Prescribing Information.”.

C. Carton Labeling

1. As currently presented, the statements [REDACTED] (b) (4) compete for prominence with other important information on the label such as proprietary name, established name, and strength. We recommend reducing the font size of these statements

so that this information does not compete for prominence with the proprietary name, established name, and strength.

2. As currently presented, the bolded statement “Single-Dose Vial” competes for prominence with other important information on the label such as proprietary name, established name, and strength. We recommend debolding and reducing the font size of this statement so that this information does not compete for prominence with the proprietary name, established name, and strength.
3. As currently presented, the strength statement lacks prominence and legibility on the principal display panel (PDP). Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter. Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., net quantity statement, NDC code, etc.).
4. The terminology within the recommended dosage statement is inconsistent with the terminology in the Prescribing Information. To ensure consistency with the terminology in the Prescribing Information, we recommend revising the (b) (4) statement to “Dosage: See Prescribing Information.”.
5. The statement (b) (4) on the side panel is duplicative with the statement on the PDP and contributes to label clutter, which may cause important information to be overlooked. We recommend removing the statement (b) (4) from the side panel.
6. As currently presented, the bolded statements (b) (4) and “Contents:” compete for prominence with other important information on the label. The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. We recommend debolding these statements so that this information does not compete for prominence with other important information.
7. As currently presented, important storage conditions may be overlooked. The storage condition “Refrigerate” should be bolded so that this important

information is not overlooked which could lead to deteriorated drug medication errors. We recommend revising to: "Storage: Refrigerate at 2°C to 8°C (36°F to 46°F) in original carton."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rytelo received on June 16, 2023 and September 18, 2023 from Geron Corporation.

Table 2. Relevant Product Information for Rytelo	
Initial Approval Date	N/A
Active Ingredient	imetelstat
Indication	TRADENAME is indicated 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).
Route of Administration	Intravenous infusion
Dosage Form	for Injection
Strength	47 mg/vial and 188 mg/vial
Dose and Frequency	The recommended dosage of TRADENAME is 7.1 mg/kg administered as an intravenous infusion over 2 hours every 4 weeks. Continue treatment as long as the patient continues to benefit and does not experience unacceptable toxicity.
How Supplied	<p>TRADENAME (imetelstat) for injection is a white to off-white or slightly yellow, lyophilized powder supplied in a single-dose vial. Each carton contains one single-dose vial.</p> <ul style="list-style-type: none"> • NDC 82959-112-01: Contains one TRADENAME 47 mg vial (equivalent to 50 mg imetelstat sodium) • NDC 82959-111-01: Contains one TRADENAME 188 mg vial (equivalent to 200 mg imetelstat sodium)
Storage	<p>Store vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton.</p> <p>Do not freeze.</p> <p>No preservative.</p>
Container Closure	<p>Single-use, (b) (4) glass vial with elastomeric stopper, and aluminum seal with a plastic cap.</p> <ul style="list-style-type: none"> • 47 mg: (b) (4) flip-off cap • 188 mg: (b) (4) flip-off cap <p>The secondary packaging consists of a pre-printed individual unit carton which provides additional protection to the glass vial during handling.</p>

	<p>The individual cartons are suitable for refrigerated use and have [REDACTED] (b) (4)</p> <p>Each vial is individually packed within a cardboard carton, which also includes the Package Insert.</p>
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APPENDIX B. PREVIOUS DMEPA REVIEWS

On July 25, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, 'Rytelo', 'imetelstat', and '217779'. Our search identified no previous reviews.

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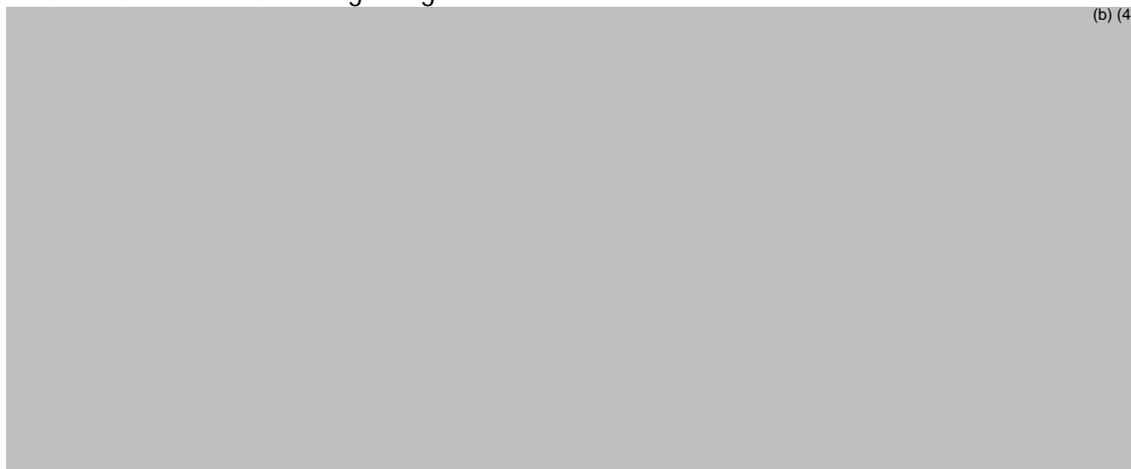
APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Rytelo labels and labeling submitted by Geron Corporation.

- Container label received on June 16, 2023
- Carton labeling received on June 16, 2023
- Prescribing Information (Image not shown) received on June 16, 2023, available from <\\CDSESUB1\EVSPROD\nda217779\0004\m1\us\114-labeling\draft\labeling\draft-labeling-text-uspi-pdf.pdf>
- Patient Information (Image not shown) received on June 16, 2023, available from <\\CDSESUB1\EVSPROD\nda217779\0004\m1\us\114-labeling\draft\labeling\draft-labeling-text-ppi-pdf.pdf>

F.2 Label and Labeling Images



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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CLINICAL INSPECTION SUMMARY

Date	November 22, 2023
From	Anthony Orenca, M.D., Ph.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Jenn Sellers, M.D., Ph.D., F.A.A.P., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Nina Kim, M.D., Clinical Reviewer E. Dianne Pulte, M.D., Clinical Reviewer Lori Ehrlich, M.D., Ph.D., Medical Team Leader Kelly Norsworthy, M.D. Deputy Director R. Angelo de Claro, M.D. Division Director Saumya Nathan, Senior Regulatory Health Project Manager Division of Hematologic Malignancies I Office of Oncology Drugs
NDA	NDA 217779
Applicant	Geron Corporation
Drug	RYTELO™ (imetelstat)
NME	Yes
Classification	Telomerase inhibitor
Proposed Indications	Treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk myelodysplastic syndromes who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents.
Review Type	Standard Review
Consultation Request Date	July 7, 2023
Summary Goal Date	November 22, 2023. Extension: November 30, 2023.
Action Goal Date	June 16, 2024
PDUFA Date	June 16, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study 63935937MDS3001 were submitted to the Agency in support of a New Drug Application for imetelstat, proposed for the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk myelodysplastic syndromes who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents. Three clinical investigators were inspected: Maria Diez Campelo, M.D. (Spain), Valeria Santini, M.D. (Italy), and Azra Raza, M.D. (New York City).

Based on the inspection results, the studies appear to have been conducted adequately and the study data derived from the clinical investigator sites are considered reliable. The clinical data submitted to the Agency for assessment appear acceptable in support of the proposed indication.

II. BACKGROUND

Imetelstat is a first-in-class telomerase inhibitor that was granted Orphan Drug Designation (ODD) (#15-5014) on 23 December 2015 for the treatment of myelodysplastic syndrome (MDS) as well as Fast Track designation for MDS on 27 October 2017.

The sponsor seeks approval to market imetelstat for the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk myelodysplastic syndromes who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA).

Study 63935937MDS3001

Study 63935937MDS3001 was a Phase 2 to 3, multicenter study of imetelstat in red blood cell transfusion-dependent subjects with low or intermediate-1 risk myelodysplastic syndrome that was relapsed/refractory to or ineligible for ESA treatment. The study consisted of two parts, the Phase 2 (Part 1) and Phase 3 (Part 2).

Phase 2 study:

The Phase 2 was an open-label, single-arm study to assess the efficacy and safety of imetelstat. The Phase 2 study consisted of 3 phases: a screening Phase of up to 28 days during which subject eligibility was reviewed and approved by the Sponsor prior to Cycle 1 Day 1 (C1D1), a treatment Phase that extended from C1D1 until progressive disease, unacceptable toxicity, or withdrawal of consent, and a post-treatment Follow-up Phase which continued until death, lost to follow-up, withdrawal of consent, or the 'End of the Study', whichever occurred first. The 'End of the Study' was defined as 2 years after the randomization of the last subject in the Phase 3 main study or until the Sponsor terminated the study, whichever came first.

The primary objective of the Phase 2 study was to evaluate the efficacy and safety of imetelstat in transfusion-dependent subjects with low or intermediate-1 risk myelodysplastic syndrome that was relapsed/refractory to ESA treatment.

The primary efficacy was evaluated by the proportion of subjects achieving red blood cell transfusion independence lasting at least any consecutive 8-week and 24-week period, starting from Study Day 1 until subsequent anti-cancer therapy, if any.

Efficacy evaluation also included time to the 8-week or 24-week red blood cell transfusion independence, duration of red blood cell transfusion independence, rate of HI-E*, rates of complete response, partial response, or modified complete response, per modified International Working Group (2006), overall survival, progression free survival, time to progression to acute myeloid leukemia, and amount and relative change in units of red blood cell transfusions.

An ad hoc analysis of HI-E* response using the International Working Group 2018 criteria was also performed [*Hematologic improvement-erythroid (HI-E) response is defined as (i) a hemoglobin increase of at least 1.5 g/dL above the pretreatment level and lasts at least 8 weeks or (ii) a reduction of at least 4 units of RBC transfusion units/8 weeks compared with the prior RBC transfusion burden (criterion adapted from the modified International Working Group 2006)].

The study was conducted at 48 study sites in 9 countries. The first subject enrolled was on December 11, 2015. The last subject enrolled was on March 1, 2018. The data cutoff date (for primary analysis) was on October 13, 2022. For the Phase 2 study, there were 57 subjects analyzed for this submission.

Phase 3 study:

The Phase 3 component study was a double-blind, randomized, placebo-controlled study to compare the efficacy of imotelstat with placebo. The Phase 3 study consisted of three phases: a screening phase of up to 28 days during which subject eligibility was reviewed and approved by the sponsor prior to randomization; a treatment phase that extended from Cycle 1 Day 1 until disease progression or unacceptable toxicity, or withdrawal of consent; and a posttreatment follow-up phase which continued until death, lost to follow-up, withdrawal of consent, or the End of the Study (whichever occurs first). The End of the Study was defined as two years after the randomization of the last subject in the main Phase 3 study or anytime the sponsor terminates the study, whichever came first.

All subjects receiving study drug (imotelstat or placebo) were premedicated with an antihistamine and a corticosteroid (hydrocortisone 100 to 200 mg or equivalent), either intravenously or orally, to mitigate infusion reactions. The starting dose of the study drug was 7.5 mg/kg every 4 weeks.

The objective of the Phase 3 study was to compare the efficacy, in terms of red blood cell transfusion independence, of imotelstat to placebo in transfusion-dependent subjects with low or intermediate-1 risk myelodysplastic syndrome that was relapsed/refractory to ESA treatment.

The primary efficacy endpoint for the Phase 3 study was evaluated by the proportion of subjects achieving red blood cell transfusion independence lasting at least any consecutive 8-week and 24-week period, starting from Study Day 1 until subsequent anti-cancer therapy, if any. Study Day 1 for Phase 3 was defined as the day of randomization.

For the Phase 3 study, the first subject enrolled on September 11, 2019. The last subject enrolled on September 15, 2021. The data cutoff date was October 13, 2022 (primary analysis). A total of 178 subjects enrolled, 118 were randomized to receive imotelstat and 60 were randomized to receive placebo. Of the 178 enrolled subjects, 177 subjects were treated (118 subjects received imotelstat and 59 subjects received placebo).

III. RESULTS

1. Maria Diez Campelo, M.D./Site ES10002

Complejo Asistencial Universitario de Salamanca.
Hospital Clinico Hematologia
Paseo de San Vicente 58-182
Salamanca, 37007
Spain

Inspection dates: October 16-19, 2023

For Phase 2 study, the site screened 5 subjects; and enrolled 3 subjects. One subject completed the study.

For Phase 3 study, the site screened 8 subjects and enrolled 5 subjects. Four enrolled subjects completed the study.

Ethics committee approvals, study correspondence, subject case history, drug accountability records, facility adequacy, staff qualifications, and monitoring procedures were reviewed.

This inspection covered study inclusion and exclusion criteria, randomization procedures where applicable, the safety of study subjects along with adverse event and serious adverse event reporting, medical progress notes, protocol deviations, subject eligibility, investigational drug product accountability, protocol compliance, and the verification of source documentation related to study endpoints.

Adverse event and serious adverse reporting appeared adequate and consistent with the study protocol requirement and the case report form reports. The primary efficacy endpoint data were verifiable. There was no evidence of under-reporting of adverse events.

Study data derived from Dr. Campelo's site are considered reliable.

2. Valeria Santini, M.D./Site IT10002

Azienda Ospedaliero-Universitaria Careggi, Largo Giovanni
Alessandro Brambilla 3
Florence, Florence, 50134
Italy

Inspection dates: September 11-15, 2023

For Phase 2 study, there was one subject screened and enrolled, Subject # (b) (6). The subject was discontinued from treatment in (b) (6) due to an SAE of pneumonia with secondary sepsis. The subject's date of death was (b) (6). For Phase 2, progress notes were handwritten in a medical record packet for Subject # (b) (6).

For Phase 3 study, 15 subjects were screened, seven subjects were enrolled and randomized, with one subject, Subject # (b) (6), still receiving treatment. There were two deaths after discontinuation of the investigational drug product (Subject # (b) (6) and Subject # (b) (6)). The Phase 3 portion of the study was ongoing. The site documented progress notes on a hospital letter head and maintained in the subject records. All subjects were recruited from the hospital.

At the inspection close-out, good documentation practices were discussed regarding a late serious adverse event reporting. Subject # (b) (6) experienced severe aortic insufficiency on (b) (6). The site was informed on (b) (6), but did not notify the sponsor until July 6, 2020, which was outside the 24-hour period of site awareness as per protocol. A site formal retraining occurred later, on March 26, 2021, about safety reporting requirements.

All adverse events and serious adverse events were reported in the submission. The primary efficacy endpoint data were verifiable.

The clinical site data from Dr. Santini are considered acceptable for the proposed low- to intermediate-1 risk myelodysplastic syndrome therapeutic indication and appear reliable.

3. Azra Raza, M.D. /Site US10021

Columbia University Medical Center – Herbert Irving Pavilion
161 Fort Washington Ave
New York, NY 10032

Inspection dates: October 5-12, 2023

For Phase 2 study, four subjects were enrolled and participated in the treatment phase. All discontinued from the study treatment.

For Phase 3 study, two subjects were enrolled and participated in the treatment phase. These two subjects completed the study treatment.

The inspection covered subject eligibility, informed consent, Institutional Review Board correspondence, study approvals, study monitoring, primary efficacy endpoint, adverse events, case report forms, protocol deviations, investigational product accountability, and the training of study staff.

Other documentations reviewed at Dr. Raza's study site included the following: sponsor correspondences' financial disclosure forms; training information; monitoring letters and correspondences, and notes to file.

The inspection reviewed six enrolled subject records along with their corresponding informed consent documents. There were four subjects reported as off study, and two subjects still in follow-up.

No under reporting of serious adverse events and adverse events were found in this inspection. The primary endpoints data were verifiable for the six reviewed subjects.

Clinical data submitted to the Agency for Dr. Raza's study site are considered acceptable.

{See appended electronic signature page}

Anthony Orenca, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.

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Jenn Sellers, M.D., Ph.D., Branch Chief

Good Clinical Practice Assessment Branch

Division of Clinical Compliance Evaluation

Office of Scientific Investigations

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/s/

ANTHONY J ORENCIA
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