RYTELO™
(imetelstat) for Injection 47 mg 188 mg

Introducing order sets in the EHR with RYTELO™

INDICATION

RYTELO (imetelstat) is indicated 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).

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Thrombocytopenia

RYTELO can cause thrombocytopenia based on laboratory values. In the clinical trial, new or worsening Grade 3 or 4 decreased platelets occurred in 65% of patients with MDS treated with RYTELO.

Monitor patients with thrombocytopenia for bleeding. Monitor complete blood cell counts prior to initiation of RYTELO, weekly for the first two cycles, prior to each cycle thereafter, and as clinically indicated. Administer platelet transfusions as appropriate. Delay the next cycle and resume at the same or reduced dose, or discontinue as recommended.

Please see Important Safety Information throughout and click for full Prescribing Information including Medication Guide.

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Important Considerations

Background

This document is intended to provide organizations with sample content for consideration in creating their own order sets in their electronic health record (EHR) systems with RYTELO™ for adult patients with low- to intermediate-1 risk myelodysplastic syndromes (LR-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). The content given does not include all details in the RYTELO Prescribing Information and the Medication Guide, and the clinical data included are only examples. Each organization must determine the final information to include based on its expectations, goals, and governing EHR principles.

The information in this document will not work for other conditions, treatments, or therapeutic areas. **This document is not intended to provide any clinical advice or recommendations, which are solely the responsibility of the organization.**

The considerations in this document are suggestions and not all considerations will apply to every organization. Naming conventions of the order set categories vary by EHR system and local governing EHR principles. Any sample content in this document that is not part of an organization's standard EHR order set should be excluded or modified accordingly and independently reviewed by the organization for clinical appropriateness. Any questions should be directed to the appropriate EHR service provider. **The organization is solely responsible for implementing, testing, monitoring, and the ongoing operation of any EHR tools.**

Please consult the RYTELO Prescribing Information for more information.

Notes

- **The organization shall be solely responsible for the implementation, testing, and monitoring of the information to ensure proper orientation in each organization's EHR system.**
- Capabilities, functionality, and setup (customization) for each EHR system may vary. Geron shall not be responsible for revising the information it provides to any organization if the customer modifies or changes its software, or the configuration of its EHR system, after such time as the information has been initially provided by Geron.
- While EHRs may assist providers in identifying appropriate patients for consideration of assessment, treatment, and referral, the decision and action should ultimately be decided by each organization in consultation with the patient, after a review of the patient's records to determine eligibility, and Geron shall have no liability thereto.
- This information has not been designed for, and is not a tool and/or solution for, meeting Meaningful Use, Advancing Care Information, and/or any other quality/accreditation requirement.
- All trademarks are property of their respective owners. Reference to these products is not intended to imply affiliation with or sponsorship of Geron and/or its affiliates.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Neutropenia

RYTELO can cause neutropenia based on laboratory values. In the clinical trial, new or worsening Grade 3 or 4 decreased neutrophils occurred in 72% of patients with MDS treated with RYTELO.

Important Considerations (cont'd)

Considerations

- EHRs have order set catalogs listing all current, as well as retired and inactive, order sets. Existing order sets may serve as a foundation to create new order sets, as many order set components may be used for different indications, diseases, and conditions.
- The organization may license order sets created by third parties. These may also be used as a foundational order set and customized to include new therapies and indications.
- Depending on the EHR, order sets may have a specific name:
  - Epic®: Beacon™ protocols/order sets
  - Oracle Cerner®: PowerPlans
  - OncoEMR®: Regimens
  - iKnowMed℠: Regimens
- A wizard may be available to help guide the organization through the order set build process. The sample content in this document has been classified using the most common categories found in EHR order sets. Local governing EHR principles may deviate from the standard categories provided.
- Some EHRs use reusable groups of similar orders (eg, all premedications are created first and then placed in multiple order sets). Check if existing category groups are available, as updating a category group may impact the content of other order sets that include the category group.
- Medication records in the EHR are provided by third-party compendia companies (eg, First Databank, Multum, and Medi-Span). They typically include the medication profile, National Drug Codes (NDCs), and detailed medication information and contribute to patient safety by offering clinical decision support (for example, alerts for potential drug-drug and drug-allergy interactions). The organization and the EHR vendor may allow for adding helpful reference links to the medication record in the EHR.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Neutropenia (cont'd)

Monitor patients with Grade 3 or 4 neutropenia for infections, including sepsis. Monitor complete blood cell counts prior to initiation of RYTELO, weekly for the first two cycles, prior to each cycle thereafter, and as clinically indicated. Administer growth factors and anti-infective therapies for treatment or prophylaxis as appropriate. Delay the next cycle and resume at the same or reduced dose, or discontinue as recommended.

Please see Important Safety Information throughout and click for full Prescribing Information including Medication Guide.

RYTELO™ (imetelstat) for Injection 47 mg 188 mg

Sample Content for Order Sets

Regimen Name
RYTELO (imetelstat) IV infusion for LR-MDS with transfusion-dependent anemia and ESA-relapsed/refractory/ineligible

Regimen Description
RYTELO (imetelstat) for treatment of adult patients with low- to intermediate-1 risk myelodysplastic syndromes (LR-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). The recommended dosage of RYTELO is 7.1 mg/kg administered as an intravenous infusion over 2 hours every 4 weeks.

References
RYTELO (imetelstat) Prescribing Information, including Medication Guide:
https://pi.Geron.com/products/US/pi/rytelo_pi.pdf

Regimen Keywords
RYTELO, imetelstat, transfusion-dependent anemia, 2L, second line, LR-MDS, failure ESA, ineligible for ESA

Recommended Dosage
The recommended dosage of RYTELO (imetelstat) is 7.1 mg/kg administered as an intravenous infusion over 2 hours every 4 weeks. Discontinue RYTELO if a patient does not experience a decrease in red blood cell transfusion burden after 24 weeks of treatment (administration of 6 doses) or if unacceptable toxicity occurs at any time [see the DOSAGE AND ADMINISTRATION (2.3) section of the Prescribing Information].

Treatment Calendar

Component	Dosing	Administration
RYTELO (imetelstat)	7.1 mg/kg administered as an intravenous infusion over 2 hours every 4 weeks	Day 1, every 4 weeks
Discontinue RYTELO if a patient does not experience a decrease in red blood cell transfusion burden after 24 weeks of treatment (administration of 6 doses) or if unacceptable toxicity occurs at any time.		

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Infusion-Related Reactions

RYTELO can cause infusion-related reactions. In the clinical trial, infusion-related reactions occurred in 8% of patients with MDS treated with RYTELO; Grade 3 or 4 infusion-related reactions occurred in 1.7%, including hypertensive crisis (0.8%). The most common infusion-related reaction was headache (4.2%). Infusion-related reactions usually occur during or shortly after the end of the infusion.

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Sample Content for Order Sets (cont'd)

Premedications

- At least 30 minutes prior to dosing with RYTELO (imetelstat), premedicate patients with diphenhydramine (25 mg to 50 mg) and hydrocortisone (100 mg to 200 mg), or equivalent, orally or intravenously to prevent or reduce potential infusion-related reactions.
- Monitor patients for adverse reactions for at least 1 hour after the infusion has been completed [see the Warnings and Precautions (5.3) and Adverse Reactions (6.1) sections of the Prescribing Information].

Treatment Conditions

Note: May also be referred to as *Treatment Parameters*, *Monitoring Conditions*, or *ISI*.

Dosage Modifications for Adverse Reactions

- Recommended dose reductions for Grade 3 and Grade 4 adverse reactions are in Table 1.
- The management of Grade 3 and Grade 4 adverse reactions may require temporary dose delay, dose reduction, or treatment discontinuation and are presented in Table 2 and Table 3.
- **RYTELO (imetelstat) treatment should be permanently discontinued if the patient cannot tolerate the lowest dose level of 4.4 mg/kg.**

Table 1: Recommended Dose Reduction for RYTELO for Grade 3 and Grade 4 Adverse Reactions

Dose Reduction	Dose Every 4 Weeks
First dose reduction	5.6 mg/kg
Second dose reduction	4.4 mg/kg

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Infusion-Related Reactions (cont'd)

Premedicate patients at least 30 minutes prior to infusion with diphenhydramine and hydrocortisone as recommended and monitor patients for one hour following the infusion as recommended. Manage symptoms of infusion-related reactions with supportive care and infusion interruptions, decrease infusion rate, or permanently discontinue as recommended.

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Sample Content for Order Sets (cont'd)

Dosage Modifications for Adverse Reactions (cont'd)

Dosage Modifications for Hematologic (Grade 3 and Grade 4) Adverse Reactions

- Monitor complete blood cell counts prior to administration of RYTELO, weekly for the first 2 cycles, prior to each cycle thereafter, and as clinically indicated.
- Delay the next cycle if absolute neutrophil count is less than 1 x 10^9/L or platelets are less than 50 x 10^9/L. Modify dose as described in Table 2.

Table 2: Dosage Modifications for Patients With Hematologic Adverse Reactions (Grade 3 and Grade 4)

Adverse Reaction	Severity Grade[a]	Occurrence	Treatment Modification
Thrombocytopenia [see the WARNINGS AND PRECAUTIONS (5.1) section of the Prescribing Information]	Grade 3	First	Delay RYTELO until recovery of platelets to 50 x 10^9/L; restart at same dose level.
		Second and Third	Delay RYTELO until recovery of platelets to 50 x 10^9/L; restart at 1 dose level lower.
		Fourth	Discontinue RYTELO.
	Grade 4	First and Second	Delay RYTELO until recovery of platelets to 50 x 10^9/L; restart at 1 dose level lower.
		Third	Discontinue RYTELO.
Neutropenia [see the WARNINGS AND PRECAUTIONS (5.2) section of the Prescribing Information]	Grade 3	First	Delay RYTELO until recovery of ANC to 1 x 10^9/L; restart at same dose level.
		Second and Third	Delay RYTELO until recovery of ANC to 1 x 10^9/L; restart at one dose level lower.
		Fourth	Discontinue RYTELO.
	Grade 4	First and Second	Delay RYTELO until recovery of ANC to 1 x 10^9/L; restart at one dose level lower.
		Third	Discontinue RYTELO.

Abbreviation: ANC, absolute neutrophil count.

[a]Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Embryo-Fetal Toxicity

RYTELO can cause embryo-fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RYTELO and for 1 week after the last dose.

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Sample Content for Order Sets (cont'd)

Dosage Modifications for Adverse Reactions (cont'd)

Dosage Modifications for Non-hematologic Adverse Reactions

Dosage modifications for infusion-related reactions and other adverse drug reactions, including elevated liver function tests, are described in Table 3.

Table 3: Dosage Modifications for Patients With Non-hematologic Adverse Reactions

Adverse Reaction	Severity Grade[a]	Occurrence	Treatment Modification
Infusion-related reactions [see the WARNINGS AND PRECAUTIONS (5.3) section of the Prescribing Information]	Grade 2 or 3	First and Second	Interrupt the RYTELO infusion until resolution of the adverse reaction or until the intensity of the reaction decreases to Grade 1; restart infusion at 50% of the infusion rate administered prior to the adverse reaction.
		Third	For Grade 2, stop infusion. May restart at next cycle. For Grade 3, permanently discontinue RYTELO.
	Grade 4	First	Stop infusion, administer supportive care as appropriate, and permanently discontinue RYTELO.
Other adverse reactions including elevated LFTs [see the ADVERSE REACTIONS (6.1) section of the Prescribing Information]	Grade 3 or 4	First and Second	Delay RYTELO until recovery of adverse reactions to Grade 1 or baseline; restart at 1 dose level lower.
		Third	Permanently discontinue RYTELO.

Abbreviation: LFTs, liver function tests.

[a]Severity based on National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS

Serious adverse reactions occurred in 32% of patients who received RYTELO. Serious adverse reactions in >2% of patients included sepsis (4.2%), fracture (3.4%), cardiac failure (2.5%), and hemorrhage (2.5%). Fatal adverse reactions occurred in 0.8% of patients who received RYTELO, including sepsis (0.8%).

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Sample Content for Order Sets (cont'd)

Nursing Orders

Note: May also be referred to as *Administration* (see section 2.4 Preparation and Administration of the Prescribing Information).

Preparation and Administration

- RYTELO (imetelstat) is provided as a lyophilized powder in a single-dose vial for intravenous infusion only and must be reconstituted and diluted prior to administration.
- Use aseptic technique to prepare RYTELO.
- RYTELO does not contain a preservative.

Reconstitution

- Calculate the dose of RYTELO needed (total mg) based on the patient's body weight (kg).
- Determine the number of RYTELO vials needed to achieve the required dose (total mg) per Table 4. More than 1 vial may be needed to achieve a full dose.
- Remove the RYTELO vials from the refrigerator and allow the vials to sit for 10 minutes to 15 minutes (not to exceed 30 minutes) to adjust to room temperature, 20 °C to 25 °C (68 °F to 77 °F), before use.
- Reconstitute each vial of RYTELO with the volume of 0.9% Sodium Chloride Injection provided in Table 4 directly onto the lyophilized powder to obtain a concentration of 31.4 mg/mL of imetelstat.

Table 4: Reconstitution Volumes

Strength[a]	Volume of 0.9% Sodium Chloride Injection for Reconstitution per Vial	Final Concentration of Reconstituted Solution per Vial	Deliverable Volume per Vial
47 mg	1.8 mL	31.4 mg/mL[b]	1.5 mL
188 mg	6.3 mL	31.4 mg/mL[b]	6 mL

[a]Recommended to use the appropriate combination of vial strengths to most closely match the intended dose based on the patient's weight.

[b]Each vial contains an overfill to account for loss of liquid during preparation and extraction of the reconstituted solution, resulting in the final concentration.

IMPORTANT SAFETY INFORMATION (cont'd)

ADVERSE REACTIONS (cont'd)

Most common adverse reactions (≥10% with a difference between arms of >5% compared to placebo), including laboratory abnormalities, were decreased platelets, decreased white blood cells, decreased neutrophils, increased AST, increased alkaline phosphatase, increased ALT, fatigue, prolonged partial thromboplastin time, arthralgia/myalgia, COVID-19 infections, and headache.

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Sample Content for Order Sets (cont'd)

Reconstitution (cont'd)

- Swirl each vial gently to avoid foaming until the powder is fully reconstituted (not to exceed 15 minutes). Do not shake.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution in each vial should appear as a clear to slightly hazy solution, essentially free of visible contaminants, particles and/or particulates. Do not use if discoloration or particulate matter is present.
- Use the reconstituted solution immediately to prepare the RYTELO diluted solution in the infusion bag.

Dilution

- Calculate the required volume of the reconstituted RYTELO solution needed to obtain the appropriate dose according to the patient's body weight.
- Withdraw a volume equal to the required reconstituted RYTELO solution from a 500 mL infusion bag of 0.9% Sodium Chloride Injection and discard it.
- Add the required volume of reconstituted RYTELO solution into the infusion bag so that the total final volume of RYTELO solution in the bag is approximately 500 mL. Discard any unused portion of the reconstituted solution remaining in each vial.
- Gently invert the infusion bag at least 5 times to ensure that the reconstituted RYTELO is well-mixed. Do not shake the infusion bag prior to administration.

Diluted RYTELO Solution Storage

- If not used immediately, ensure that the diluted solution for infusion is used within the total timeframes specified below, according to storage temperature:
  - *When stored at room temperature 20 °C to 25 °C (68 °F to 77 °F)*:
    The total time from the reconstitution of RYTELO to completion of the intravenous infusion should not exceed 18 hours from the time of reconstitution.
  - *When stored refrigerated 2 °C to 8 °C (36 °F to 46 °F)*:
    The total time from the reconstitution of RYTELO to completion of the intravenous infusion should not exceed 48 hours from the time of reconstitution.

Administration

- Administer the diluted RYTELO solution by intravenous infusion only over a period of 2 hours.

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS

Thrombocytopenia

RYTELO can cause thrombocytopenia based on laboratory values. In the clinical trial, new or worsening Grade 3 or 4 decreased platelets occurred in 65% of patients with MDS treated with RYTELO.

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Sample Content for Order Sets (cont'd)

Dosage Forms and Strengths

- For injection: 47 mg of imetelstat supplied as a white to off-white or slightly yellow lyophilized powder in a single-dose vial for reconstitution.
  - NDC 82959-112-01
- For injection: 188 mg of imetelstat supplied as a white to off-white or slightly yellow lyophilized powder in a single-dose vial for reconstitution.
  - NDC 82959-111-01

Warnings and Precautions

- Thrombocytopenia
- Neutropenia
- Infusion-Related Reactions
- Embryo-Fetal Toxicity

See Section 5 of the Prescribing Information for full details.

Adverse Reactions

See Section 6 of the Prescribing Information for full details.

Use in Specific Populations

See Section 8 of the Prescribing Information for full details.

Helpful Links

Consider adding links such as this in the references section of the medication record:

- RYTELO Prescribing Information, including Medication Guide: https://pi.Geron.com/products/US/pi/rytelo_pi.pdf

IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Thrombocytopenia (cont'd)

Monitor patients with thrombocytopenia for bleeding. Monitor complete blood cell counts prior to initiation of RYTELO, weekly for the first two cycles, prior to each cycle thereafter, and as clinically indicated. Administer platelet transfusions as appropriate. Delay the next cycle and resume at the same or reduced dose, or discontinue as recommended.

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Important Safety Information

WARNINGS AND PRECAUTIONS

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RYTELO can cause neutropenia based on laboratory values. In the clinical trial, new or worsening Grade 3 or 4 decreased neutrophils occurred in 72% of patients with MDS treated with RYTELO.

Monitor patients with Grade 3 or 4 neutropenia for infections, including sepsis. Monitor complete blood cell counts prior to initiation of RYTELO, weekly for the first two cycles, prior to each cycle thereafter, and as clinically indicated. Administer growth factors and anti-infective therapies for treatment or prophylaxis as appropriate. Delay the next cycle and resume at the same or reduced dose, or discontinue as recommended.

Infusion-Related Reactions

RYTELO can cause infusion-related reactions. In the clinical trial, infusion-related reactions occurred in 8% of patients with MDS treated with RYTELO; Grade 3 or 4 infusion-related reactions occurred in 1.7%, including hypertensive crisis (0.8%). The most common infusion-related reaction was headache (4.2%). Infusion-related reactions usually occur during or shortly after the end of the infusion.

Premedicate patients at least 30 minutes prior to infusion with diphenhydramine and hydrocortisone as recommended and monitor patients for one hour following the infusion as recommended. Manage symptoms of infusion-related reactions with supportive care and infusion interruptions, decrease infusion rate, or permanently discontinue as recommended.

Embryo-Fetal Toxicity

RYTELO can cause embryo-fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with RYTELO and for 1 week after the last dose.

ADVERSE REACTIONS

Serious adverse reactions occurred in 32% of patients who received RYTELO. Serious adverse reactions in >2% of patients included sepsis (4.2%), fracture (3.4%), cardiac failure (2.5%), and hemorrhage (2.5%). Fatal adverse reactions occurred in 0.8% of patients who received RYTELO, including sepsis (0.8%).

Most common adverse reactions (≥10% with a difference between arms of >5% compared to placebo), including laboratory abnormalities, were decreased platelets, decreased white blood cells, decreased neutrophils, increased AST, increased alkaline phosphatase, increased ALT, fatigue, prolonged partial thromboplastin time, arthralgia/myalgia, COVID-19 infections, and headache.

Please see RYTELO (imetelstat) full Prescribing Information, including Medication Guide.

Reference: 1. RYTELO. Package insert. Geron Corporation; 2024.

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