RYTELO™
(imetelstat) for Injection 47 mg 188 mg

Guide to Monitoring and Managing Adverse Reactions

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 additional Important Safety Information on pages 12-13 and full Prescribing Information and Medication Guide.

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RYTELO safety data

The efficacy and safety of RYTELO were evaluated in a phase 3, randomized, double-blind, placebo-controlled, multicenter trial that enrolled adult patients with International Prognostic Scoring System (IPSS) low- to intermediate-1 risk MDS who were transfusion-dependent and relapsed or refractory to or ineligible for erythropoiesis-stimulating agents (ESAs). The safety analysis set (N=177) included all patients who received at least 1 dose of study drug.[1]

Adverse reactions (≥5%) in patients with MDS who received RYTELO with a difference between arms of >2% compared to placebo[1]

	RYTELO (n=118)		PLACEBO (n=59)	
Adverse Reaction	**All Grades %**	**Grade 3 or 4 %**	**All Grades %**	**Grade 3 or 4 %**
General disorders and administrative site conditions				
Fatigue*	29	0	20	3.4
Musculoskeletal and connective tissue disorders				
Arthralgia/myalgia†	25	2.5	19	5
Infections and infestations				
COVID-19‡	19	1.7	14	5
Urinary tract infection§	9	2.5	7	0
Nervous system disorders				
Headache	13	0.8	5	0
Syncope‖	7	1.7	1.7	0

- Clinically relevant adverse reactions in <5% of patients who received RYTELO included febrile neutropenia, sepsis, gastrointestinal hemorrhage, and hypertension[1]

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.
*Fatigue: asthenia, fatigue, and malaise.[1]
†Arthralgia/myalgia: arthralgia, bone pain, back pain, neck pain, musculoskeletal pain, pain, pain in jaw, pelvic pain, non-cardiac chest pain, myalgia, and pain in extremity.[1]
‡COVID-19: COVID-19, asymptomatic COVID-19, SARS-CoV-2 antibody test positive, and COVID-19 pneumonia.[1]
§Urinary tract infection: cystitis, *Escherichia* urinary tract infection, renal abscess, and urinary tract infection.[1]
‖Syncope: pre-syncope, syncope, and fall.[1]

RYTELO safety data (cont'd)

Adverse reactions (≥5%) in patients with MDS who received RYTELO with a difference between arms of >2% compared to placebo (cont'd)[1]

	RYTELO (n=118)		PLACEBO (n=59)	
Adverse Reaction	**All Grades %**	**Grades 3 or 4 %**	**All Grades %**	**Grades 3 or 4 %**
Immune system disorders				
Infusion-related reactions¶	8	1.7	3.4	0
Respiratory, thoracic, and mediastinal disorders				
Epistaxis	7	0	0	0
Vascular disorders				
Hematoma	6	0	0	0
Skin and subcutaneous tissue disorders				
Pruritus	6	0	1.7	0
Cardiac disorders				
Atrial arrhythmia#	6	1.7	3.4	1.7
Injury, poisoning, and procedural complications				
Fractures**	5	3.4	1.7	1.7

¶Infusion-related reactions: abdominal pain, arthralgia, asthenia, back pain, bone pain, diarrhea, erythema, headache, hypertensive crisis, malaise, non-cardiac chest pain, pruritus, and urticaria. Only events considered related to infusion-related reactions are included.[1]
#Atrial arrhythmia: atrial fibrillation and atrial flutter.[1]
**Fractures: hand fracture, hip fracture, lumbar vertebral fracture, femur fracture, humerus fracture, and thoracic vertebral fracture.[1]

Treatment was discontinued due to adverse reactions in 15% (n=17) of patients receiving RYTELO[1]

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Select laboratory abnormalities observed with RYTELO[2]

Select laboratory abnormalities worsened since baseline in phase 3 IMerge trial[2]

Laboratory Parameter	RYTELO (n=118)			PLACEBO (n=59)		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematology						
Thrombocytopenia	113 (95.7)	51 (43.2)	26 (22)	20 (33.9)	3 (5.1)	2 (3.4)
Neutropenia	108 (91.5)	55 (46.6)	29 (24.6)	28 (47.5)	3 (5.1)	1 (1.7)
PTT prolonged	25 (25.8)	1 (1)	0	9 (18)	2 (4)	0
Chemistry						
AST increased	57 (48.3)	1 (0.8)	0	13 (22)	1 (1.7)	0
ALP increased	53 (44.9)	0	0	7 (11.9)	0	0
ALT increased	50 (42.7)	4 (3.4)	0	22 (37.3)	3 (5.1)	0

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PTT, partial thromboplastin time.
Graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

- **7.6% (n=9) of patients taking RYTELO discontinued due to cytopenias[2]**

Clinical consequences of cytopenias in all patients across IMerge trial[2]

Event	RYTELO (n=118)		PLACEBO (n=59)	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Bleeding events*	25 (21.2)	3 (2.5)	7 (11.9)	1 (1.7)
Infections†	50 (42.4)	12 (10.2)	20 (33.9)	8 (13.6)
Febrile neutropenia‡	1 (0.8)	1 (0.8)	0	0

- **Clinical consequences of Grade ≥3 cytopenias were comparable to placebo[2]**
- 17.8% (n=21) of RYTELO-treated patients received a median of 1 platelet transfusion vs 1.7% (n=1) on placebo[2]
- 34.7% (n=41) of RYTELO-treated patients received growth factor support vs 3.3% (n=2) on placebo[2]

TI, transfusion independence.
*No Grade ≥3 bleeding events associated with Grades 3-4 thrombocytopenia.[2]
†Three patients in the RYTELO group had Grades 3-4 infections concurrent with Grades 3-4 neutropenia.[2]
‡Occurred day 33, lasted 8 days; assessed by investigator as possibly related to RYTELO; patient subsequently achieved TI >40 weeks and remains on treatment at data cutoff.[3]

In most patients, Grade ≥3 cytopenias occurred early and returned to Grade ≤2 within 4 weeks with dose modification[2]

Time to onset and resolution of cytopenias[1,2]

Grades 3-4 Cytopenias Per Lab Value	RYTELO (n=118)	PLACEBO (n=59)
Thrombocytopenia events		
Median time to onset, weeks (range)	6.0 (1.7-88.3)	15.1 (6.4-40.6)
Median duration, weeks (range)	1.3 (0.1-12.6)	2.0 (0.3-11.6)
Returned to Grade ≤2 within 4 weeks, %	86.3	44.4
Neutropenia events		
Median time to onset, weeks (range)	4.6 (1.0-81.0)	13.0 (3.0-23.0)
Median duration, weeks (range)	1.9 (0-15.9)	2.2 (1.0-4.6)
Returned to Grade ≤2 within 4 weeks, %	81.0	50.0

- The median time to onset of cytopenias occurred during the first 4.6-6 weeks[1]

In >80% of patients, platelets recovered to ≥50,000/mm^3 and neutrophils recovered to ≥1000/mm^3 within 4 weeks[3,4,§]

§All data presented indicate Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2.

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Analyses of ARs seen in IMerge phase 3 trial of RYTELO (n=118)

Thrombocytopenia[1,2]

65% of patients had new or worsening Grade 3 or Grade 4 thrombocytopenia

For patients experiencing thrombocytopenia:

- 6 weeks was the median time to onset of Grade 3 or Grade 4 thrombocytopenia
- 10 days was the median duration of Grade 3 or Grade 4 thrombocytopenia
- 3.4% of patients permanently discontinued RYTELO due to thrombocytopenia
- 46.6% of patients had dose delays due to thrombocytopenia
- 22.9% of patients had dose reductions due to thrombocytopenia

Neutropenia[1,2]

72% of patients had new or worsening Grade 3 or Grade 4 neutropenia

For patients experiencing neutropenia:

- 4 weeks and 4 days was the median time to onset of Grade 3 or Grade 4 neutropenia
- 13 days was the median duration of Grade 3 or Grade 4 neutropenia
- 5.1% of patients permanently discontinued RYTELO due to neutropenia
- 50.8% of patients had dose delays due to neutropenia
- 33.1% of patients had dose reductions due to neutropenia

Infusion-related reactions[1,2,*]

8% of patients had infusion-related reactions

For patients experiencing infusion-related reactions:

- Infusion-related reactions usually occur during or shortly after the end of the infusion
- Reactions are Grade 1 or 2 in severity
- 4.2% of patients experienced headache, which was the most common reaction
- Hypertensive crisis (0.8%) was also observed

Administer the following pre-treatment medications at least 30 minutes prior to dosing to prevent or reduce potential infusion-related reactions:

- Diphenhydramine (or equivalent) 25 mg to 50 mg, intravenously or orally
- Hydrocortisone (or equivalent) 100 mg to 200 mg, intravenously or orally

*Infusion-related reactions consisted of headache, asthenia, malaise, non-cardiac chest pain, arthralgia, back pain, bone pain, abdominal pain, diarrhea, erythema, pruritus, urticaria, and hypertensive crisis. Only events considered related to infusion-related reactions are included.[1]

Management of ARs may require dose modifications[1]

The recommended dose of RYTELO is 7.1 mg/kg.[1]

Management of Grade ≥3 ARs may require temporary dose delay, dose reduction, or treatment discontinuation.[1]

Dose delay

- 80% (n=94) of patients receiving RYTELO had a dose delay due to TEAEs vs 23.7% (n=14) on placebo[1,2]

NOTE: Length of dose delay is patient dependent and may vary.

Dose reduction

- 49% (n=58) of patients receiving RYTELO had a dose reduction due to TEAEs vs 6.8% (n=4) on placebo[1,2]

NOTE: RYTELO should be permanently discontinued if the patient cannot tolerate the lowest dose level of 4.4 mg/kg.[1]

- 15% (n=17) of patients receiving RYTELO discontinued treatment due to adverse reactions[1]
- 7.6% (n=9) of patients discontinued due to cytopenias[2]
- Administer growth factors and anti-infective therapies for treatment or prophylaxis as appropriate[1]
- **Discontinue RYTELO if a patient does not experience a decrease in RBC transfusion burden after 24 weeks of treatment (administration of 6 doses) or if unacceptable toxicity occurs at any time[1]**

Please see the full Prescribing Information for details on specific dose modifications for adverse reactions

Monitoring

All patients receiving RYTELO treatment should be monitored for bleeding, infections, and elevated LFTs.[1]

A complete blood cell count should be conducted weekly prior to infusion for the first 2 cycles, prior to each cycle thereafter, and as clinically indicated for Grade 3 or Grade 4 thrombocytopenia and/or neutropenia.[1]

- Patients with Grade 3 or Grade 4 thrombocytopenia should be monitored for bleeding events as a precaution
- As a precaution, patients with Grade 3 or Grade 4 neutropenia should be monitored for infections, including sepsis
- Monitor LFTs prior to administration of RYTELO, weekly for the first cycle, prior to each cycle thereafter, and as clinically indicated
- Monitor patients for ARs for at least 1 hour after the infusion has been completed

LFT, liver function test; TEAE, treatment-emergent adverse event.

Please see Important Safety Information on pages 12-13 and full Prescribing Information and Medication Guide.

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Dose modifications for patients with hematologic ARs[1,*]

Recommended dose reductions for Grade 3 or Grade 4 ARs[1]

Dose reduction	Dose every 4 weeks
First dose reduction	5.6 mg/kg
Second dose reduction	4.4 mg/kg

Thrombocytopenia

Grade 3†

1st Occurrence

Delay RYTELO until recovery of platelets to **50 x 10^9/L**; restart at same dose level

2nd Occurrence

Delay RYTELO until recovery of platelets to **50 x 10^9/L**; restart at one dose level lower

3rd Occurrence

Delay RYTELO until recovery of platelets to **50 x 10^9/L**; restart at one dose level lower

4th Occurrence

Discontinue RYTELO

Grade 4‡

1st Occurrence

Delay RYTELO until recovery of platelets to **50 x 10^9/L**; restart at one dose level lower

2nd Occurrence

Delay RYTELO until recovery of platelets to **50 x 10^9/L**; restart at one dose level lower

3rd Occurrence

Discontinue RYTELO

HCP, healthcare provider.

*Severity based on National Cancer Institute CTCAE Version 4.03.[5]

†Grade 3 thrombocytopenia defined as platelet counts <50-25 x 10^9/L.[5]

‡Grade 4 thrombocytopenia defined as platelet counts <25 x 10^9/L.[5]

Neutropenia

Grade 3§

1st Occurrence

Delay RYTELO until recovery of ANC to **1 x 10^9/L**; restart at same dose level

2nd Occurrence

Delay RYTELO until recovery of ANC to **1 x 10^9/L**; restart at one dose level lower

3rd Occurrence

Delay RYTELO until recovery of ANC to **1 x 10^9/L**; restart at one dose level lower

4th Occurrence

Discontinue RYTELO

Grade 4‖

1st Occurrence

Delay RYTELO until recovery of ANC to **1 x 10^9/L**; restart at one dose level lower

2nd Occurrence

Delay RYTELO until recovery of ANC to **1 x 10^9/L**; restart at one dose level lower

3rd Occurrence

Discontinue RYTELO

ANC, absolute neutrophil count.

§Grade 3 neutropenia defined as neutrophil counts <1-0.5 x 10^9/L.[5]

‖Grade 4 neutropenia defined as neutrophil counts <0.5 x 10^9/L.[5]

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Dose modifications for patients with non-hematologic ARs[1,*]

Management of Grade ≥3 ARs may require temporary dose delay, dose reduction, or treatment discontinuation according to HCP discretion.[1]

- The length of the dose delay is patient dependent and may vary. Please see "Dosage and Administration" section of the full Prescribing Information for more information

Other adverse drug reactions including elevated LFTs

Grade 3

1st Occurrence

Delay RYTELO until recovery of adverse reactions to **Grade 1 or baseline**; restart at one dose level lower

2nd Occurrence

Delay RYTELO until recovery of adverse reactions to **Grade 1 or baseline**; restart at one dose level lower

3rd Occurrence

Permanently **discontinue** RYTELO

Grade 4

1st Occurrence

Delay RYTELO until recovery of adverse reactions to **Grade 1 or baseline**; restart at one dose level lower

2nd Occurrence

Delay RYTELO until recovery of adverse reactions to **Grade 1 or baseline**; restart at one dose level lower

3rd Occurrence

Permanently **discontinue** RYTELO

LFT, liver function test.
*Severity based on National Cancer Institute CTCAE Version 4.03.[5]

Infusion-related reactions

Grade 2 or Grade 3†

1st Occurrence

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

2nd Occurrence

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

3rd Occurrence

For Grade 2, **stop** infusion. May **restart** at next cycle. For Grade 3, permanently **discontinue** RYTELO

Grade 4‡

1st Occurrence

Stop infusion, administer supportive care as appropriate, and permanently **discontinue** RYTELO

†Grade 3 infusion-related reactions defined as prolonged recurrence of symptoms following initial improvement.[5]
‡Grade 4 infusion-related reactions defined as having life-threatening consequences with urgent intervention indicated.[3]

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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.

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.

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.

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%).

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 full Prescribing Information and Medication Guide.

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A patient support program for RYTELO

REACH4 RYTELO™

Learn more at RYTELOHCP.com

For patient support resources, click, call, or email
1-844-4RYTELO | **support@reach4rytelo.com**

INDICATION

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Please see additional Important Safety Information on pages 12-13 and full Prescribing Information and Medication Guide.

References: 1. RYTELO. Prescribing information. Geron Corp.; 2024. **2.** Data on file. Geron Corporation. Foster City, CA. **3.** Platzbecker U, Santini V, Fenaux P, et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2024;(Supplement)403(10423):249-260. **4.** Platzbecker U, Santini V, Fenaux P, et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2024;403(10423):249-260. **5.** US Department of Health and Human Services. National Institutes of Health. CTCAE v4.03. June 14, 2010.

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