Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Imetelstat (Rytelo)	MP-RX-FP-157-24	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B Drugs

Service Description

This document addresses the use of imetelstat (Rytelo®), an oligonucleotide telomerase inhibitor approved by the Food and Drug Administration (FDA) 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).

Background Information

Myelodysplastic syndromes (MDS) are a group of heterogeneous hematologic malignancies characterized by clonal abnormalities in blood cell production, leading to cytopenias, abnormal cellular maturation, and varying risks of progression to acute myeloid leukemia (AML). While many patients with MDS exhibit symptoms such as anemia, bleeding, or infections, others may remain asymptomatic.

The prognosis for MDS patients varies significantly, with outcomes largely determined by specific bone marrow, blood, cytogenetic, and molecular features. Patients are generally classified into lower-risk or higher-risk categories based on these features, guiding treatment strategies accordingly. The Revised International Prognostic Scoring System assigns a score of ≤3.5 to classify lower-risk MDS patients.

Most MDS cases fall into the "lower-risk" category (LR-MDS), signifying a reduced immediate risk of death or progression to AML. However, anemia and complications from cytopenias, transfusions, and inflammation can adversely impact comorbidities, potentially lowering quality of life (QoL) and increasing mortality compared to the general population. After diagnosing and assessing risk, treatment is individualized, with the focus for LR-MDS patients on managing symptoms and enhancing QoL. Given the typically long survival with malignant hematopoiesis, treatment often centers on addressing cytopenias—particularly anemia—and managing complications like iron overload.

A major complication in LR-MDS is progressive anemia, eventually necessitating regular red blood cell (RBC) transfusions. Erythropoiesis-stimulating agents (ESAs) are the standard first-line treatment for symptomatic anemia in LR-MDS, as they stimulate RBC production in the bone marrow. However, response rates to ESAs vary widely, with 30-60% of patients responding for 1-2 years. Over time, all patients eventually become resistant to ESA therapy. Those with low RBC transfusion needs and serum erythropoietin (sEPO) levels below 200-500 mU/mL are more likely to respond to ESAs, whereas patients with high transfusion requirements or sEPO levels above 500 mU/mL have a significantly lower likelihood (<10%) of achieving a response.

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Imetelstat (Rytelo), a telomerase inhibitor, has received FDA approval for treating adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) who suffer from transfusion-dependent anemia and require at least four red blood cell (RBC) units over eight weeks. This approval is specifically for those who have not responded to, have lost response to, or are ineligible for erythropoiesis-stimulating agents (ESAs). The approval was granted based on the phase 3 IMerge trial (NCT02598661), a double-blind, multicenter, placebo-controlled study.

The IMerge trial involved 178 patients (aged ≥18 years) with low or intermediate-1 risk MDS, categorized according to the International Prognostic Scoring System (IPSS) criteria, who were either ESA-relapsed, ESA-refractory, or ESA-ineligible. Participants were randomized to receive either imetelstat (118 patients) or a placebo (60 patients) until disease progression, unacceptable toxicity, or withdrawal of consent. The primary endpoint was the achievement of an 8-week period of RBC transfusion independence (RBC-TI), defined as the absence of RBC transfusions for at least eight consecutive weeks from randomization until any subsequent anti-cancer therapy.

The median follow-up was 19.5 months for the imetelstat group and 17.5 months for the placebo group. The results showed that 40% of patients in the imetelstat group achieved RBC-TI for at least eight weeks, compared to 15% in the placebo group, highlighting a significant difference in efficacy (rate difference 25%; p=0.0008). Additionally, RBC transfusion independence lasting at least 24 weeks was achieved by 28.0% of imetelstat-treated patients (95% CI, 20.1%-37.0%) compared to 3.3% in the placebo group (95% CI, 0.4%-11.5%; P <.001). The median duration of RBC-TI was approximately one year for 8-week responders and 1.5 years for 24-week responders in the imetelstat group.

Subgroup analysis revealed that among patients with serum erythropoietin (sEPO) levels greater than 500 mU/mL, 26.9% achieved RBC-TI at 8 weeks with imetelstat (vs. 9.1% with placebo; P = .107), and 15.4% achieved RBC-TI at 24 weeks (vs. 0.0% with placebo; P = .050). However, safety data indicated that 91% of patients treated with imetelstat experienced grade 3-4 treatment-emergent adverse events, compared to 47% of patients receiving placebo. The most common adverse events in the imetelstat group were neutropenia (68% vs. 3% in the placebo group) and thrombocytopenia (62% vs. 8% in the placebo group).

Approved Indications

Imetelstat (Rytelo®) is indicated by the FDA 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).

Other Uses

None

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J3490	Unclassified drugs
J9999	Not otherwise classified, antineoplastic drugs
C9399	Unclassified drugs

ICD-10	Description
C93.10	Chronic myelomonocytic leukemia not having achieved remission
D46.0	Refractory anemia without ring sideroblasts
D46.1	Refractory anemia with ring sideroblasts
D46.20	Refractory anemia with excess of blasts, unspecified
D46.4	Refractory anemia, unspecified
D46.9	Myelodysplastic syndrome, unspecified
D46.A	Refractory cytopenia with multilineage dysplasia
D46.B	Refractory cytopenia with multilineage dysplasia and ring sideroblasts
D46.C	Myelodysplastic syndrome with isolated del(5q) chromosomal abnormality
D46.Z	Other myelodysplastic syndromes

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

imetelstat (Rytelo®)

A. Criteria For Initial Approval (*Provider must submit documentation [such as office chart notes, lab results, pathology reports, imaging studies, and any other pertinent clinical information] supporting the patient's diagnosis for the drug and confirming that the patient has met **all** approval criteria.)*

i. The patient has myelodysplastic syndrome (MDS) that is classified as low- to intermediate-1 risk, defined by **one** of the following:
   A. International Prognostic Scoring System (IPSS): Low or intermediate-1 risk (defined as a score of 0 to 1); **OR**
   B. Revised International Prognostic Scoring System (IPSS-R): Very low, low, intermediate risk (defined as a score of 0 to 4.5); **OR**
   C. WHO-Based Prognostic Scoring System (WPSS): very low, low, intermediate (Score 0 to 2)

AND

ii. The patient has anemia that has required 4 or more RBC units over 8 weeks;

AND

iii. The patient is using an ESA and has either not responded adequately or has lost response to the ESA, as defined by one of the following:
   A. Hb rise <1.5 g/dL after at least 8 weeks of treatment
   B. No improvement in transfusion frequency after at least 8 weeks of treatment

OR

iv. The patient is ineligible to receive an ESA, defined by having EPO levels > 500 mU/mL

B. Criteria For Continuation of Therapy

i. MMM considers continuation of imetelstat (Rytelo®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when the following evidence is submitted:
   A. The patient has experienced a decrease in red blood cell (RBC) transfusion burden after 24 weeks (6 months of therapy); **AND**
   B. The patient has not experienced unacceptable toxicity.

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C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

D. Conditions Not Covered

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Anemia not related to LR-MDS
ii. When the above criteria are not met, and for all other indications.

Limits or Restrictions

A. Therapeutic Alternatives

The list below includes preferred alternative therapies recommended in the approval criteria and may be subject to prior authorization.

i. N/A

B. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug	Recommended Dosing Schedule
imetelstat (Rytelo®)	7.1 mg/kg administered as an intravenous infusion over 2 hours every 4 weeks.
Exceptions	
None	

Reference Information

1. Brunner, A.M., Leitch, H.A., van de Loosdrecht, A.A. *et al.* Management of patients with lower-risk myelodysplastic syndromes. *Blood Cancer J.* 12, 166 (2022). https://doi.org/10.1038/s41408-022-00765-8
2. Hattakitpanitchakul S, Kobbuaklee S, Wudhikarn K, Polprasert C. Prediction of Response to Erythropoiesis Stimulating Agents in Low-Risk Myelodysplastic Syndromes. Asian Pac J Cancer Prev. 2021 Dec 1;22(12):4037-4042. doi: 10.31557/APJCP.2021.22.12.4037. PMID: 34967586; PMCID: PMC9080375.
3. Imetelstat (Rytelo®) [package insert]. Geron Corporation; 06/2024.

4. Sekres MA, Platzbecker U. Treatment of lower-risk myelodysplastic syndromes (MDS). UpToDate. Last update: 06/20/2024
5. Meunier M, Park S. Lower-risk myelodysplastic syndromes: Current treatment options for anemia. EJHaem. 2022 Aug 12;3(4):1091-1099. doi: 10.1002/jha2.523. PMID: 36467818; PMCID: PMC9713208.
6. National Comprehensive Cancer Network. (2024). *Myielodisplastic Syndromes (version 3.2024)*. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf
7. 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. doi:10.1016/S0140-6736(23)01724-5
8. Sekres MA, Platzbecker U. Myelodysplastic syndromes/neoplasms (MDS): Management of hematologic complications in lower-risk MDS. UptoDate. Last update 06/11/2024.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	New Medical Policy creation.	9/16/2024	10/8/2024

Revised: 06/13/2024