Medical Policy Bulletin

Title:
Imetelstat (Rytelo)
Policy #:
MA08.177

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

MEDICALLY NECESSARY

INITIAL THERAPY
Imetelstat (Rytelo™) is considered medically necessary and, therefore, covered for the treatment of adult individuals with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia when dosing and frequency requirements and **ALL** of the following criteria are met:

- Diagnosis of MDS confirmed by bone marrow aspirate and/or biopsy
- Individual has required transfusion of four or more red blood cell (RBC) units over 8 weeks **AND** pretransfusion hemoglobin is 9.0 g/dL or less
- Individual with lower risk disease (i.e., very low, low, intermediate) as assessed by validated rating index/scale (e.g., International Prognostic Scoring System-revised [IPSS-R]) and **ONE** of the following:
    - Disease associated with symptomatic anemia **WITH** del(5q), with or without one other cytogenetic abnormality (except those involving chromosome 7) and **ONE** of the following:
        - Following no response to or relapse after lenalidomide if poor probability to respond to immunosuppressive therapy (IST) (e.g., older age, high-risk mutations)
        - Following no response to or relapse after an erythropoiesis-stimulating agent (ESA) if poor probability to respond to IST (e.g., older age, high-risk mutations)
        - Following no response to or relapse after lenalidomide, followed by no response to or intolerance or relapse after IST

        - Following no response to or relapse after an ESA with serum erythropoietin 500 mU/mL or less, followed by no response to or intolerance or relapse after IST
    - Disease associated with symptomatic anemia **WITHOUT** del(5q), with or without other cytogenetic abnormalities and **ONE** of the following:
        - With ring sideroblasts less than 15 percent (or ring sideroblasts <5 percent with an SF3B1 mutation) and **ONE** of the following:
            1. With serum erythropoietin 500 mU/mL or less following no response to or relapse after an ESA alone, followed by no response to or relapse after an ESA with or without a G-CSF or lenalidomide
            2. With serum erythropoietin 500 mU/mL or less following no response to or relapse after an ESA alone, followed by no response to or relapse after luspatercept-aamt
            3. With serum erythropoietin 500 mU/mL or less following no response to or relapse after luspatercept-aamt, followed by no response to or relapse after an ESA with or without a G-CSF or lenalidomide
            4. With serum erythropoietin greater than 500 mU/mL and a poor probability to respond to IST (e.g., older age, high-risk mutations)
            5. With serum erythropoietin greater than 500 mU/mL following no response to or intolerance or relapse after IST
        - With ring sideroblasts 15 percent or greater (or ring sideroblasts 5 percent or greater with an SF3B1 mutation) and **ONE** of the following:
            1. Following no response to or relapse after luspatercept-aamt (National Comprehensive Cancer Network [NCCN] preferred)
            2. With serum erythropoietin 500 mU/mL or less following no response to or relapse after luspatercept-aamt, followed by no response to or relapse after an ESA with or without a G-CSF if a poor probability to respond to IST (e.g., older age, high-risk mutations)
            3. With serum erythropoietin 500 mU/mL or less following no response to or relapse after luspatercept-aamt, followed by no response to or relapse after an ESA with or without a G-CSF, followed by no response to or intolerance or relapse after IST
            4. As initial treatment if serum erythropoietin greater than 500 mU/mL (ineligible for ESAs)
            5. With serum erythropoietin greater than 500 mU/mL following no response to or relapse after luspatercept-aamt, followed by no response to or relapse after lenalidomide if a poor probability to respond to IST (e.g., older age, high-risk mutations)
            6. With serum erythropoietin greater than 500 mU/mL following no response to or relapse after luspatercept-aamt, followed by no response to or relapse after lenalidomide, followed by no response to or intolerance or relapse after IST
- Dosing and frequency: 7.1 mg/kg administered as an intravenous infusion over 2 hours every 4 weeks

CONTINUATION THERAPY

Continuation of imetelstat (Rytelo) is considered medically necessary and, therefore, covered for individuals who have demonstrated BOTH of the following, compared to baseline:

- Individual experiences a decrease in RBC transfusion burden after 24 weeks of treatment (administration of six doses)
- No unacceptable toxicity occurs at any time

EXPERIMENTAL/INVESTIGATIONAL

All other uses of imetelstat (Rytelo) are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

DOSING AND FREQUENCY REQUIREMENTS

The Company reserves the right to modify the Dosing and Frequency Requirements listed in this policy to ensure consistency with the most recently published recommendations for the use of imetelstat (Rytelo). Changes to these

guidelines are based on a consensus of information obtained from resources such as, but not limited to: the FDA; Company-recognized authoritative pharmacology compendia; or published peer-reviewed clinical research. The professional provider must supply supporting documentation (i.e., published peer-reviewed literature) in order to request coverage for an amount of imetelstat (Rytelo) outside of the Dosing and Frequency Requirements listed in this policy. For a list of Company-recognized pharmacology compendia, view our policy on off-label coverage for prescription drugs and biologics.

Accurate member information is necessary for the Company to approve the requested dose and frequency of this drug. If the member's dose, frequency, or regimen changes (based on factors such as changes in member weight or incomplete therapeutic response), the provider must submit those changes to the Company for a new approval based on those changes as part of the precertification process. The Company reserves the right to conduct postpayment review and audit procedures for any claims submitted for imetelstat (Rytelo).

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

Guidelines

There is no Medicare coverage criteria addressing this service; therefore, the Company policy is applicable.

BENEFIT APPLICATION

Subject to the terms and conditions of the applicable benefit contract, imetelstat (Rytelo) is covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in the medical policy are met.

INTERNATIONAL PROGNOSTIC SCORING SYSTEM-REVISED

International Prognostic Score System-Revised (IPSS-R) score values

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	N/A	Good	N/A	Intermediate	Poor	Very poor
Bone marrow blast, percent	2 or less	N/A	>2 to <5	N/A	5 to 10	>10	N/A
Hemoglobin	10 or more	N/A	8 to <10	<8	N/A	N/A	N/A
Platelets	100 or more	50 to <100	<50	N/A	N/A	N/A	N/A
Absolute neutrophil count	0.8 or more	<0.8	N/A	N/A	N/A	N/A	N/A

Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120(12):2454-2465.

IPSS-R prognostic risk categories/scores

Risk category	Risk score
Very low	1.5 or less
Low	>1.5 to 3
Intermediate	>3 to 4.5
High	>4.5-6
Very high	>6

Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120(12):2454-2465.

INTERNATIONAL CONSENSUS CLASSIFICATION SYSTEM

	Dysplastic lineages	Cytopenias	Cytoses	Bone marrow (BM) and peripheral blood (PB) blasts	Cytogenetics	Mutations
Myelodysplastic syndrome (MDS) with mutated SF3B1 (MDS-SF3B1)	Typically 1 or greater	1 or greater	0	<5 percent BM <2 percent PB	Any except isolated del(5q), -7/del(7q), abn3q26.2, or complex	SF3B1 (10 percent or greater variant allele frequency [VAF]) without multi-hit TP53, or RUNX1
MDS with del(5q) [MDS-del(5q)]	Typically 1 or greater	1 or greater	Thrombocytosis allowed	<5 percent BM <2 percent PB	del(5q), with up to 1 additional, except -7/del(7q)	Any, except multi-hit PT53
MDS, not otherwise specified (NOS), without dysplasia	0	1 or greater	0	<5 percent BM <2 percent PB	-7/del(7q) or complex	Any, except multi-hit TP53 or SF3B1 (10 percent or greater VAF)
MDS, NOS with single lineage dysplasia	1	1 or greater	0	<5 percent BM <2 percent PB	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit TP53; not meeting criteria for MDS-SF3B1
MDS, NOS with multilineage dysplasia	2 or greater	1 or greater	0	<5 percent BM <2 percent PB	Any, except not meeting criteria for MDS-del(5q)	Any, except multi-hit TP53; not meeting criteria for MDS-SF3B1
MDS with excel blasts (MDS-EB)	Typically 1 or greater	1 or greater	0	5-9 percent BM 2-9 percent PB	Any	Any, except multi-hit TP53

Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022;140(11):1200-1228.

US FOOD AND DRUG ADMINISTRATION STATUS

Imetelstat (Rytelo) was approved by the US Food and Drug Administration (FDA) on June 6, 2024, for the treatment

of adult individuals with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring four or more red blood cell units over 8 weeks who have not responded to, have lost response to, or are ineligible for erythropoiesis-stimulating agents (ESA).

PEDIATRIC USE
The safety and effectiveness of imetelstat (Rytelo) have not been established in the pediatric population.

Description

Myelodysplastic syndromes (MDS), or myelodysplastic neoplasms (MDN), are conditions that are characterized by abnormal (dysplastic) cells in the bone marrow that result in the production of defective blood cells and/or low volume of one or more types of blood cells. Approximately 10,000 individuals are diagnosed with MDS in the United States annually. MDS is considered to be a type of cancer. MDS is not common in individuals younger than 50 years old, and the risk of developing MDS increases as the individual ages. Most cases of MDS have no identifiable cause, but there are some risk factors for the development of MDS including exposure to tobacco smoke, ionizing radiation, and exposure to certain chemicals or heavy metals. Secondary MDS can result after an individual is treated with chemotherapy and/or radiation therapy as part of a cancer regimen. Genetic changes, some inherited, and others acquired, may lead to the development of MDS. The symptoms of MDS, such as lethargy, weight loss, frequent infections, and easy bleeding or bruising, are very general, so may be attributed to another cause. Lab tests may demonstrate low levels of red blood cells most often, but also white blood cells and/or platelets. These signs can also be attributed to other causes. A bone marrow biopsy will demonstrate immature cells (blasts) in the marrow. Long term, MDS may progress to acute myeloid leukemia (AML; about one in three individuals will be affected) or bone marrow failure.

Tests are done to look for specific gene or chromosome changes that might lead to the development of MDS (e.g., SF3B1, ASXL1, RUNX1). These, along with lab tests, are used for risk stratification of the individual, determining the treatment course, and predicting an individual's prognosis. Examples of risk stratification scoring systems include the Revised International Prognostic Scoring System (IPSS-R) and the Molecular International Prognostic Scoring System (IPSS-M). These scoring systems are used to categorize the individual as either lower risk MDS or higher risk MDS based on bone marrow characteristics, peripheral blood results, cytogenetics, and molecular features.

Standard therapies for MDS are often supportive, not treatments of the MDS. Individuals with MDS often require the transfusion of red blood cells (RBCs) and/or platelets. Erythropoiesis-stimulating agents (ESAs) (e.g., epoetin alfa, epoetin beta, darbepoetin alfa), are commonly ordered to encourage the production of RBCs. ESAs may not be appropriate for all individuals (e.g., individuals with endogenous erythropoietin concentration >500 mU/mL), or the individual may develop a resistance to the effects of the ESA, leading to the need for alternative therapies. Treatment with granulocyte-colony stimulating factors (G-CSF) (e.g., filgrastim, pegfilgrastim) or granulocyte-macrophage colony stimulating factors (GM-CSF) (e.g., sargramostim) are commonly ordered to encourage the production of various white blood cells (WBCs). Thrombopoietin receptor agonists (TPO-RAs) (e.g., romiplostim, eltrombopag) are administered to encourage platelet (plt) production. A chelating agent (e.g., deferoxamine, deferasirox) may be given if the individual has undergone multiple RBC transfusions over a period of years, and has developed iron overload. There are also some therapies that are used to treat MDS. Hypomethylating agents (e.g., azacitidine, decitabine), a type of chemotherapy, are some of the most effective drugs in the treatment of MDS, but do not work for everyone or can stop working as time progresses. For higher risk individuals, other chemotherapies may be used (e.g., cytarabine). Lenalidomide, an immunomodulator, is one type of targeted drug therapy that can be used to treat individuals with certain MDS genetic changes or karyotypes (e.g., del[5q]). Undergoing a hematopoietic stem cell transplant (HSCT) may lead to a long-term remission of MDS, but this requires the individual to tolerate an intense treatment regimen prior to receiving the transplant.

Imetelstat (Rytelo) is an oligonucleotide telomerase inhibitor that binds to the template region of the RNA component of human telomerase (hTR) resulting in inhibited telomerase enzymatic activity and prevention of telomere binding. Increased telomerase activity and hTR reverse transcriptase (hTERT) RNA expression have been reported in MDS and malignant stem cells and progenitor cells. Imetelstat (Rytelo) is believed to reduce telomere length, reduce proliferation of malignant stem and progenitor cells, and induce apoptotic cell death.

CLINICAL TRIAL

IMerge
The efficacy and safety of imetelstat (Rytelo) in transfusion-dependent individuals with low to intermediate-1 risk MDS

that was relapsed or refractory to ESAs was evaluated in a phase 2 to 3, multicenter, open-label, single-arm clinical trial titled Study to Evaluate Imetelstat (GRN163L) in Participants With International Prognostic Scoring System (IPSS) Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) (NCT02598661). Transfusion dependence was defined as requiring at least four units of RBCs transfused over an 8-week period during the 16 weeks prior to study entry. The pretransfusion hemoglobin (Hgb) must have been 9.0 g/dL or less to count towards the four-unit total. For the phase 3 portion of the clinical trial, the participants could not have the del(5q) karyotype, and could not have previously been treated with a hypomethylating agent (HMA) or lenalidomide.

The phase 2 portion of the clinical trial enrolled 57 individuals. All participants received imetelstat (Rytelo), 7.5 mg/kg as an intravenous (IV) infusion, every 4 weeks until there was disease progression, unacceptable toxicity, consent withdrawal, or it was deemed there was a lack of a response. The primary endpoint was the percentage of participants who were transfusion independent during any consecutive 8-week period over the course of 12 months. Key secondary endpoints included percentage of individuals who achieved 24 weeks of transfusion independence, time to the 8-week transfusion independence, duration of transfusion independence, and measures surrounding disease progression and adverse events. At the time of clinical cutoff, 14 of 57 individuals (25 percent) were continuing to receive the drug. There were multiple reasons for participant attrition: lack of efficacy (n=16), adverse events (n=14), individual consent withdrawal/refusal (n=6), disease progression (including transformation to AML in two individuals) (n=3), death (n=2), relapse (n=1), and physician decision (n=1). Thirty-seven percent (21/57) of participants achieved the primary endpoint of transfusion independence for 8 consecutive weeks and 23 percent (13/57) achieved 24-week transfusion independence. The median time to achieve 8-week transfusion independence was 8.3 weeks (range, 0.1 to 100.6 weeks for all 57 individuals). The median duration of transfusion independence was 65 weeks (range, 17 to 140.9 weeks for all 57 individuals). For disease activity, the overall response rate (ORR) for all 57 individuals was 19 percent (9 percent [5/57] complete responses [CR], 11 percent [6/57] marrow CR [mCR], no partial responses [PR]). Of the individuals who experienced a CR or mCR, 46 percent had complete resolution of dysplasia. The majority of adverse events experienced by participants were hematologic. The percentages of all 57 individuals who experienced thrombocytopenia, neutropenia, or anemia were 61, 67, and 23, respectively. The percentage of all 57 individuals who experienced grade 3 or higher thrombocytopenia, neutropenia, or anemia were 54, 60, and 19, respectively. Most of these hematologic events resolved to grade 2 or lower within 4 weeks.

The phase 3 portion of the clinical trial was double blinded and placebo controlled. The study enrolled 178 individuals, with participants randomly assigned in a 2:1 ratio to imetelstat (Rytelo) or placebo. Participants received imetelstat (Rytelo) 7.5 mg/kg or placebo as an IV infusion every 4 weeks until there was disease progression, unacceptable toxicity, consent withdrawal, or it was deemed there was a lack of a response. The primary and secondary endpoints for the phase 3 portion of the clinical trial were similar to those for the phase 2 portion. Of the total participants, 118 were randomly assigned to imetelstat (Rytelo) and 60 were randomly assigned to placebo (one individual did not receive treatment so was not included in the results). At the time of clinical cutoff, 27 of 118 individuals (23 percent) were continuing to receive imetelstat (Rytelo) and 14 of 59 (24 percent) were continuing to receive placebo. The reasons for attrition were similar to those from the phase 2 portion of the clinical trial. There was one death in each cohort during treatment or within 30 days of stopping treatment. For the primary endpoint, 40 percent (47/118) of individuals in the study cohort versus 15 percent (9/59) in the placebo cohort achieved at least 8 weeks of transfusion independence (rate difference, 25 percent; 9.9 to 35.9; P=0.0008). The percentage of individuals who achieved 24-week transfusion independence was 28 percent (33/118) in the study cohort versus 3 percent (2/59) in the placebo cohort (rate difference, 25 percent; 12.6 to 34.2; P=0.0001). In long-term follow-up, 18 percent (21/118) of the study cohort versus 2 percent (1/59) of the placebo group achieved 1-year transfusion independence (p=0.0023). Of individuals who achieved 8-week transfusion independence, the median duration of transfusion independence was 51.6 weeks (range 26.9 to 83.9 weeks) in the study group (47/118) versus 13.3 weeks (range, 8.0 to 24.9 weeks) in the placebo group (9/59) (P=0.0007). The majority of adverse events experienced by participants were hematologic. Grade 3 or 4 treatment-emergent adverse events occurred in 91 percent (107/118) of the study group versus 47 percent (28/59) of the placebo group, with 68 percent (80/118) of the study group experiencing neutropenia and 62 percent (73/118) experiencing thrombocytopenia. Most of these hematologic events resolved to grade 2 or lower within 4 weeks. Two percent of individuals in both cohorts experienced progression to AML (2/118 vs 1/59).

In the study cohort, 62 percent (73/117) of individuals were ring sideroblast positive and 37 percent (44/117) were ring sideroblast negative. In the placebo cohort, 62 percent (37/60) were ring sideroblast positive and 38 percent (23/60) were ring sideroblast negative. The primary endpoint was reached in 45 percent (33/73) of individuals who were ring sideroblast positive and 32 percent (14/44) of individuals who were ring sideroblast negative in the study cohort. The primary endpoint was reached in 19 percent (7/37) of individuals who were ring sideroblast positive and 9 percent (2/23) who were ring sideroblast negative in the placebo cohort. Continuous transfusion independence for at least 24 weeks was achieved by 33 percent (24/73) of individuals who were ring sideroblast positive and 20 percent (9/44) of individuals who were ring sideroblast negative in the study cohort. Continuous transfusion independence for at least 24 weeks was achieved by 5 percent (2/37) of individuals who were ring sideroblast positive and none (0/23) of individuals who were ring sideroblast negative in the placebo cohort. Among individuals with evaluable mutation

data (110/118 [93 percent] in the study cohort; 55/60 [92 percent] in the placebo cohort), SF3B1, TET2, DNMT3A, and ASXL1 were the most frequently mutated genes. Reductions in variant allele frequency (VAF) of these mutations was greater in the study cohort than in the placebo cohort (*P*<0.001, *P*=0.032, *P*=0.019, *P*=0.146, respectively).

OFF-LABEL INDICATIONS

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)
N/A

ICD - 10 Procedure Code Number(s)
N/A

ICD - 10 Diagnosis Code Number(s)
N/A

HCPCS Level II Code Number(s)
J0870 Injection, imetelstat, 1 mg

Revenue Code Number(s)
N/A

Policy History

Revisions From MA08.177:

03/20/2026	The policy will become effective 03/20/2026. The following new policy has been developed to communicate the Company's coverage criteria for imetelstat (Rytelo™).

Version Effective Date:
03/20/2026
Version Issued Date:
03/20/2026
Version Reissued Date:
N/A