imetelstat (Rytelo™)

Medicare Advantage Medical Policy # 100
Original Effective Date: 06/01/2025
Current Effective Date: 06/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Health Plan may consider the use of imetelstat (Rytelo™)‡ for the treatment of myelodysplastic syndromes (MDS) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for imetelstat (Rytelo) will be considered when the following criteria are met:

- Initial (6 months)
  - Patient is ≥ 18 years of age; AND
  - Patient has low-to intermediate-1 risk myelodysplastic syndrome (MDS) based on one of the following:
    - Revised International Prognostic Scoring System (IPSS-R) score of 0 to 4.5; OR
    - International Prognostic Scoring System (IPSS) score 0 to 1; OR
    - World Health Organization-Based Scoring System (WPSS) score 0 to 2; AND
  - Patient has had transfusion-dependent anemia, defined as requiring transfusion of ≥ 4 red blood cell units over an 8-week period in the last 16 weeks; AND
  - According to the prescriber, patient has not responded, lost response to, or is ineligible for treatment with erythropoiesis-stimulating agents. Examples of erythropoiesis-stimulating agents include an epoetin alfa product (e.g., Epogen®, Procrit®, or Retacrit®)‡, a darbepoetin alfa product (e.g., Aranesp®)‡, or a pegylated epoetin beta product (e.g., Mircera®)‡; AND
  - Rytelo will NOT be used in combination with an erythropoiesis stimulating agent or Reblozyl; AND
  - Patient does NOT have deletion 5q [del(5q)] cytogenetic abnormalities; AND
  - Patient has an ANC > $1x10^9$/L and platelets > $50x10^9$/L; AND
  - Dose does NOT exceed 7.1 mg/kg every 4 weeks.
- Continuation (12 months)
  - Patient has received an initial authorization for Rytelo from the plan OR has provided documentation of authorization from previous Medicare Advantage plan; AND
  - Patient has experienced a decrease in transfusion burden from baseline; AND
  - Patient has an ANC > 1 x 10^9/L and platelets > 50 x 10^9/L; AND

- Dose does not exceed 7.1 mg/kg every 4 weeks.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of Rytelo when the patient has del(5q) cytogenetic abnormalities to be **not medically necessary.****

Based on review of available data, the Health Plan considers the continued use of Rytelo when the patient has not experienced a decrease in transfusion burden from baseline while on therapy to be **not medically necessary.****

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers the use of imetelstat (Rytelo) when the patient selection criteria are not met (except those noted above as **not medically necessary****) to be **investigational.***

Background/Overview

Rytelo is an oligonucleotide human telomerase inhibitor approved 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 (RBC) units over 8 weeks. It is only approved for those patients who have not responded to, have lost response to, or are ineligible for erythropoiesis-stimulating agents (ESAs). Rytelo should be dosed as 7.1 mg/kg administered intravenously over 2 hours every 4 weeks. If the patient does not experience a decrease in RBC transfusion burden after 24 weeks of treatment (6 doses) or experiences unacceptable toxicity, Rytelo should be discontinued. Additionally, patients receiving Rytelo infusions should be pre-treated with diphenhydramine and hydrocortisone to prevent or reduce potential infusion-related reactions.

Myelodysplastic syndromes (MDS) are a group of rare bone marrow disorders that cause cytopenias. Between 20-50% of patients with MDS will eventually progress to acute leukemia, but the majority succumb to bone marrow failure prior to progression to leukemia. The standard of care treatment for this condition is erythropoiesis stimulating agents (ESAs) such as epoetin alfa products (e.g., Epogen, Procrit, or Retacrit), darbepoetin alfa products (e.g., Aranesp), and pegylated epoetin beta products (e.g., Mircera). Approximately 10% of patients with MDS are unable to take ESAs for various reasons. Alternative treatments include luspatercept (Reblozyl) and hypomethylating agents (e.g., azacitidine [Vidaza®]‡, and cedazuridine-dacitabine [Inqovi®]‡). In patients with the subtype of MDS caused by the del(5q) mutation, lenalidomide (Revlimid®)‡ can be used. It should be noted that patients with this cytogenetic abnormality were excluded from trials with Rytelo.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Rytelo was approved in June 2024 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.

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Rytelo was evaluated in a randomized, double-blind, placebo-controlled, multicenter trial in 178 patients enrolled with International Prognostic Scoring System (IPSS) low- or intermediate-1 risk MDS who were transfusion-dependent (requiring $\geq$ 4 RBC units over an 8-week period during the 16 weeks prior to randomization). Eligible patients were required to have failed to respond or have lost response or be ineligible for erythropoiesis-stimulating agents; and had an ANC of 1.5 x 10^9/L or greater and platelets 75 x 10^9/L or greater. Patients were ineligible if they had del(5q) cytogenetic abnormality or had received prior treatment with lenalidomide or hypomethylating agents.

Participants were randomized in a 2:1 ratio to receive an intravenous infusion of Rytelo (n = 118) 7.1 mg/kg or placebo (n = 60) in 28-day treatment cycles until disease progression, unacceptable toxicity, or withdrawal from the study. Randomization was stratified by prior RBC transfusion burden and by IPSS risk group. All patients received supportive care, which included RBC transfusions.

Efficacy was established after a median follow up time of 19.5 months (range: 1.4 to 36.2) in the Rytelo group and 17.5 months (range: 0.7 to 34.3) in the placebo group based upon the proportion of patients who achieved $\geq$ 8 week and $\geq$ 24-week RBC-TI, defined as the absence of RBC transfusion(s) during any consecutive 8 weeks (56 days) period, and during any consecutive 24 weeks (168 days) period, respectively, from randomization until the start of subsequent anti-cancer therapy (if any). In the Rytelo group, 39.8% achieved at least 8-week RBC-TI compared to 15% in the placebo group. This corresponded to a percent difference of 24.8% (95% CI: 9.9, 36.9; $p < 0.001$). For 24-week RBC-TI, 28% of those in the Rytelo group and 3.3% in the placebo group met the criteria. This corresponds to a 24.6% difference (95% CI: 12.6, 34.2; $p < 0.001$).

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References

1. Rytelo [package insert]. Geron Corporation. Foster City, CA. Updated June 2024.
2. Rytelo New Drug Review. IPD Analytics. Updated July 2024.

Policy History

Original Effective Date: 06/01/2025
Current Effective Date: 06/01/2025
03/18/2025 UM Committee Review. New policy
Next Scheduled Review Date: 03/2026

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2024 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	NA
HCPCS	J0870
ICD-10 Diagnosis	All related diagnoses

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*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan

recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.
NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.