Clinical Policy: Remestemcel-L-rknd (Ryoncil)

Reference Number: CP.PHAR.474
Effective Date: 12.18.24
Last Review Date: 05.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

Remestemcel-L-rknd (Ryoncil®) is an allogeneic bone marrow-derived mesenchymal stem cell (MSC) therapy.

FDA Approved Indication(s)

Ryoncil is indicated for the treatment of steroid-refractory acute graft versus host disease (GVHD) in pediatric patients 2 months of age and older.

Policy/Criteria

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

It is the policy of health plans affiliated with Centene Corporation® that Ryoncil is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Acute Graft Versus Host Disease (must meet all)**:**

1. Diagnosis of grade II to IV (*see Appendix F*) acute GVHD following hematopoietic cell transplantation;
2. Disease is steroid-refractory as evidenced by any of the following (a, b, or c):
   a. Progression of acute GVHD within 3 to 5 days of therapy onset with ≥ 2 mg/kg per day of prednisone or dose equivalent corticosteroid (*see Appendix D and E*);
   b. Failure to improve within 5 to 7 days of treatment initiation with ≥ 2 mg/kg per day of prednisone or dose equivalent corticosteroid (*see Appendix D and E*);
   c. Partial response after > 28 days of immunosuppressive treatment including ≥ 2 mg/kg per day of prednisone or dose equivalent corticosteroid (*see Appendix B, D, and E*);
3. Prescribed by or in consultation with an oncologist, hematologist, or bone marrow transplant specialist;
4. Age 2 months to ≤ 17 years;
5. Documentation of member's current body weight in kg;
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 2 x 10^6 MSC/kg (1 dose) two times per week;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 1 month (8 doses)

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

A. Acute Graft Versus Host Disease (must meet all)**:**

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Ryoncil for acute GVHD and has received this medication for at least 28 days;
2. For requests extending beyond 28 days, one of the following (a or b):
   a. Member has demonstrated evidence of a partial or mixed response but not yet a complete response (*see Appendix E)*;
   b. GVHD has recurred following a complete response (*see Appendix E)*;
3. Member has not received more than 16 doses of Ryoncil;
4. If request is for a dose increase, documentation of member's current body weight in kg;
5. Request meets one of the following (a, b, or c):*
   a. For members with partial or mixed response: Dose does not exceed 2 x 10^6 MSC/kg (1 dose) per week;
   b. For recurrence of GVHD after complete response, or for requests to complete the first 28 days of treatment: Dose does not exceed 2 x 10^6 MSC/kg (1 dose) two times per week;
   c. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 1 month

Members requesting completion of the first 28 days of treatment: up to 8 doses
Members with partial or mixed response: 4 additional doses, up to a total of 12 doses
Members experiencing recurrence of GVHD after complete response: 8 additional doses, up to a total of 16 doses

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
GVHD: graft-versus-host disease
MSC: mesenchymal stem cells
NCCN: National Comprehensive Cancer Network

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Examples of corticosteroids for acute GVHD		
betamethasone, dexamethasone, prednisone, prednisolone, methylprednisone*	Dose recommendations per NCCN based on organ involvement: Upper GI only: 0.5-1 mg/kg/day methylprednisolone (or prednisone dose equivalent) Skin/lower GI/liver: 1-2 mg/kg/day methylprednisolone (or prednisone dose equivalent)	Corticosteroid dosage must be individualized and is highly variable depending on the nature and severity of the disease, route of treatment, and on patient response

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

**Off-label*

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): known hypersensitivity to dimethyl sulfoxide (DMSO) or porcine and bovine proteins
- Boxed warning(s): none reported

Appendix D: Equivalent Corticosteroid Dosages

Acute Steroid-Refractory GVHD: Equivalent Corticosteroid Dosages	
Prednisolone	5 mg PO
Prednisone	5 mg PO
Methylprednisolone	4 mg PO
Dexamethasone	0.75 mg PO
Betamethasone	0.75 mg PO

Appendix E: Measurement of Response to Therapy

Response Definitions per Pivotal Study and Prescribing Information	
Complete response	Resolution of acute GVHD in all involved organs
Partial response	Organ improvement of at least 1 stage without worsening of any other organs
Mixed response	Improvement in at least 1 evaluable organ with worsening in another
No response	No change in any organ stage in any organ system and no improvement in organ stage
Progression	Deterioration in at least 1 organ system by 1 stage or more with no improvement in any other organ

Appendix F: General Information

- Acute GVHD refers to an allogeneic inflammatory response occurring in three organs: the skin, the liver, and the gastrointestinal tract. A grading system is used to assess the severity of disease based on clinical manifestations and the extent of organ involvement. There are a number of different grading systems available (e.g., Glucksberg, modified Glucksberg, Keystone, International Bone Marrow Transplantation Registry [IBMTR], Mount Sinai Acute GvHD International Consortium [MAGIC]), none of which has been shown to be superior in predicting survival. While there are no standardized definitions for each grade across these systems, all consider grade I disease to involve only the skin. Grade II, III, and IV disease go beyond the skin and additionally involve the liver and/or gastrointestinal tract.

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Steroid-refractory acute GVHD	2 x 10^6 MSC/kg IV twice weekly (at least 3 days apart) for 4 consecutive weeks (8 infusions)	See regimen

Indication	Dosing Regimen	Maximum Dose
	Assess response 28 ± 2 days after the first dose, and administer further treatment if appropriate as described below: • If complete response, no further treatment with Ryoncil • If partial or mixed response, repeat administration of Ryoncil once a week for additional 4 weeks (i.e., 4 additional infusions) • If no response, consider alternative treatments • If GVHD recurs after complete response, repeat administration of Ryoncil twice a week for an additional 4 consecutive weeks (i.e., 8 additional infusions)	

VI. Product Availability

Cell suspension for intravenous infusion in a target concentration of 6.68 x 10^6 MSCs per mL in 3.8 mL contained in a 6 mL cryovial

VII. References

1. Ryoncil Prescribing Information. New York, NY: Mesoblast, Inc.; December 2024. Available at: https://www.fda.gov/media/184603/download. Accessed January 8, 2025.
2. National Comprehensive Cancer Network. Hematopoietic Cell Transplantation (HCT): Pre-Transplant Recipient Evaluation and Management of Graft-Versus-Host Disease Version 2.2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf. Accessed January 8, 2025.
3. Kurtzberg J, Abdel-Azim H, Carpenter P et al. A phase 3, single-arm, prospective study of remestemcel-L, ex-vivo culture-expanded adult human mesenchymal stromal cells, for the treatment of pediatric patients who failed to respond to steroid treatment for acute GVHD. Biol Blood Marrow Transplant. 2020 May; 26(5): 845-854.
4. Clinical Pharmacology [database online]. Philadelphia, PA: Elsevier; 2025. Available at: https://www.clinicalkey.com/pharmacology/. Accessed January 8, 2025.
5. Schoemans HM, Lee SJ, Ferrara JL, et al. EBMT-NIH-CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. Bone Marrow Transplant. 2018;53(11):1401–1415.
6. Oncologic Drugs Advisory Committee briefing document: Remestemcel-L for treatment of steroid refractory acute graft versus host disease in pediatric patients. Published August 13, 2020.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J3402	Injection, remestemcel-l-rknd, per therapeutic dose

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2021 annual review: per published clinical trial, revised lower age limit to 2 months; clarified approval for continued therapy would be for 4 additional doses, up to a total of 12 doses; revised reference to HIM off-label use policy from HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	02.17.21	05.21
2Q 2022 annual review: no significant changes; references reviewed and updated.	02.21.22	05.22
Template changes applied to other diagnoses/indications.	09.28.22	
2Q 2023 annual review: no significant changes as drug is not yet FDA-approved; references reviewed and updated.	01.24.23	05.23
2Q 2024 annual review: no significant changes as drug is not yet FDA-approved; references reviewed and updated.	02.07.24	05.24
2Q 2025 annual review: drug is now FDA approved – criteria updated per FDA labeling: for continued therapy, added pathway for use in cases of GVHD recurrence following complete response and revised total number of doses allowed from 12 to 16; for both initial and continued therapy, added requirement for documentation of member's current weight; references reviewed and updated.	02.11.25	05.25
HCPCS code added [J3402], removed HCPCS codes [J3590, C9399].	09.11.25	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy,

contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.