Clinical Policy: Remestemcel-L-rknd (Ryoncil)

Reference Number: PA.CP.PHAR.474
Effective Date: 06/2025
Last Review Date: 05/2025

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 PA Health & Wellness® 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*).

Approval duration: 1 month (8 doses)

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

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

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies;
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*).

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. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.PHARM.01) applies.
   Approval duration: Duration of request or 12 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

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 – PA.CP.PMN.53

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 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.

Appendix C: Contraindications/Boxed Warnings

V. Dosage and Administration

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

VI. Product Availability

Cell suspension for intravenous infusion in a target concentration of 6.68×10^6 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
J3590	Unclassified biologics
C9399	Unclassified drugs or biologicals

Reviews, Revisions, and Approvals	Date
Policy created	05/2025