CENTENE® Corporation

Clinical Policy: Remestemcel-L (Ryoncil)

Reference Number: CP.PHAR.474
Effective Date: FDA Approval Date
Last Review Date: 05.22
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 (Ryoncil™) is a cell-therapy product containing human mesenchymal stem cells (MSC).

FDA Approved Indication(s) [Pending]

Ryoncil is indicated for treatment of steroid refractory acute graft-versus-host disease (GVHD) in pediatric patients.

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*

**Criteria will mirror the clinical information from the prescribing information once FDA-approved*

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

1. Diagnosis of steroid-refractory acute GVHD (grades II to IV), post hematopoietic cell transplantation, 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*);*
2. Prescribed by or in consultation with an oncologist, hematologist, or bone marrow transplant specialist;*
3. Age 2 months to ≤ 17 years;*
4. 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 total)

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*

**Criteria will mirror the clinical information from the prescribing information once FDA-approved*

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 a covered indication and has received this medication for at least 30 days;*
2. For requests extending beyond 28 days, member has demonstrated evidence of a "partial" or "mixed" response but not yet a "complete" response (*see Appendix E)*;*
3. Member has not received more than 12 doses;*
4. Request meets one of the following (a or b):*
   a. Dose does not exceed 2 x 10^6 MSC/kg (1 dose) 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 (4 additional doses, up to a total of 12 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
Acute steroid-refractory GVHD corticosteroid and immunosuppressive therapies		
mycophenolate mofetil (Cellcept®) *(*off label indication)*	2 g/day PO in combination with cyclosporine and prednisolone.	Adults: 3 g/day PO or IV Adolescents/ children/ infants: 2 g/day PO
cyclosporine (Gengraf®, Neoral®, Sandimmune®) *(*off label indication)*	15 mg/kg PO as a single dose 4 to 12 hours before transplantation. For maintenance therapy, the initial dosage can be continued, divided into 2 equal daily doses and adjusted to achieve a predefined cyclosporine blood concentration.	The maximum dosage is dependent on indication, route of therapy, and cyclosporine serum concentrations
tacrolimus (Prograf®) *(*off label indication)*	Adults and Adolescents: A dosage of 0.1 mg/kg/day IV in 2 divided doses or Doses of 0.3	Maximum dosage for systemic formulations is dependent on indication, route of therapy, and tacrolimus serum concentrations

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	mg/kg/day PO in 2 divided doses Children: A dosage of 0.1 mg/kg/day continuous IV infusion has been utilized.	
betamethasone	Adults, Adolescents, and Children: 0.5 to 9 mg IM daily. Dose range is one-third to one-half the normal corticosteroid oral dose given every 12 hours	Adults/adolescents: 50 g/week Children: N/A
dexamethasone	Adults: Initially, 0.5 to 9 mg/day IV or IM, in divided doses. Children and Adolescents: 0.06 to 0.3 mg/kg/day or 1.2 to 10 mg/m2/day IM or IV in divided doses every 6 to 12 hours.	Dosage must be individualized and is highly variable depending on the nature and severity of the disease, route of treatment, and on patient response.
prednisone	Adults: alternating with cyclosporine has been recommended at doses of prednisone 1 mg/kg/day PO plus cyclosporine (10 mg/kg/day PO in 2 divided doses)	Corticosteroid dosage must be individualized and is highly variable depending on the nature and severity of the disease, and on patient response. There is no absolute maximum dosage.
methylprednisone *(off label indication)	Adults, Adolescents and Children: 2 to 2.5 mg/kg/day IV, tapered slowly over 2 to 3 weeks. Initial doses of 10 mg/kg/day IV have also been used. For GVHD limited to the skin, an initial dose of 1 mg/kg/day IV may be used.	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. As per NCCN there is no role for escalation beyond 2 mg/kg/day.

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.

Appendix C: Contraindications/Boxed Warnings [Pending]

- Contraindication(s): pending
- Boxed warning(s): pending

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

2014 NIH response definitions for clinical trials in GVHD	
Complete response	Complete resolution of acute GVHD manifestations in all organs, without need for secondary GVHD therapy.
Partial response	Improvement in GVHD stage from baseline in all initially affected organs, without resolution in all organs, worsening in any other GVHD target organs or need for secondary GVHD therapy
Mixed response	Complete or partial response in at least one organ accompanied by progression in another organ.
No response	Same severity of GVHD in any organ or death, or the addition of secondary GVHD therapy before day 28.
Progression	Worsening GVHD in at least 1 organ with or without improvement in any other organ.

V. Dosage and Administration [Pending]

Indication	Dosing Regimen	Maximum Dose
Steroid-refractory acute GVHD *	2 x 10^6 MSC/kg twice weekly (at least 3 days apart) for 4 weeks; if partial or mixed response 4 additional once-weekly infusions may be administered*	Pending

VI. Product Availability [Pending]

Pending

VII. References

1. National Comprehensive Cancer Network. Hematopoietic Cell Transplantation (HCT): Pre-Transplant Recipient Evaluation and Management of Graft-Versus-Host Disease Version 5.2021. Available at: https://www.nccn.org/professionals/physician_gls/pdf/hct.pdf. Accessed February 21, 2022.
2. 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.
3. Drug Monographs. Clinical Pharmacology. Tampa, FL: Gold Standard Inc.; 2020. Available at: https://www.clinicalkey.com/pharmacology/. Accessed February 21, 2022.
4. Lee SJ. Classification systems for chronic graft-versus-host disease. Blood. 2017;129(1):30–37.

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. Lee SJ, Wolff D, Kitko C, et al. Measuring therapeutic response in chronic graft-versus-host disease. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: IV. The 2014 Response Criteria Working Group report. *Biol Blood Marrow Transplant*. 2015;21(6):984–999.
7. Oncologic Drugs Advisory Committee Briefing Document: Remestemcel-L for Treatment of Steroid Refractory Acute Graft Versus Host Disease In Pediatric Patients. August 13, 2020. Available at: https://www.fda.gov/media/140996/download. Accessed February 21, 2022.

Coding Implications [Pending]
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
Pending	Pending

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created pre-emptively	03.03.20	05.20
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	

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.