Pharmacy Management Drug Policy

SUBJECT: Ryoncil (remestemcel-l-rknd)
POLICY NUMBER: PHARMACY-131
EFFECTIVE DATE: 05/2025
LAST REVIEW DATE: 06/12/2026

If the member's subscriber contract excludes coverage for a specific service or prescription drug, it is not covered under that contract. In such cases, medical or drug policy criteria are not applied. This drug policy applies to the following line/s of business:

Policy Application

Category:	☒ Commercial Group (e.g., EPO, HMO, POS, PPO)	☒ Medicare Advantage
	☒ On Exchange Qualified Health Plans (QHP)	☐ Medicare Part D
	☒ Off Exchange Direct Pay	☒ Essential Plan (EP)
	☒ Medicaid & Health and Recovery Plans (MMC/HARP)	☒ Child Health Plus (CHP)
	☐ Federal Employee Program (FEP)	☐ Ancillary Services
	☒ Dual Eligible Special Needs Plan (D-SNP)	

DESCRIPTION:

Ryoncil ™ (remestemcel-L) is an allogeneic bone marrow-derived mesenchymal stromal cell therapy indicated for the treatment of pediatric steroid-refractory acute graft-versus-host disease (SR-aGVHD) in patients 2 months ≤ 18 years of age. Ryoncil is administered via intravenous (IV) infusion, typically in a series of eight doses over four weeks.

The exact mechanism of action of Ryoncil is not fully understood; however, it is believed to function through immunomodulatory and anti-inflammatory effects. Clinical studies suggest that Ryoncil interacts with immune effector cells such as T cells and dendritic cells to reduce inflammatory cytokine production, support tissue repair, and promote immune homeostasis. These processes are the crux in the management of GVHD.

Acute GVHD is a serious and potentially life-threatening complication of allogeneic hematopoietic stem cell transplantation (HSCT) that can involve one or more organ systems (e.g., the skin, gastrointestinal tract, and liver). Steroids are the first-line treatment; however, up to 50% of pediatric patients do not adequately respond. These cases are considered steroid-refractory and are at high risk for morbidity and mortality.

Approval of Ryoncil was based on the results from a single-arm, phase III trial (MSB-GVHD001; NCT02336230) that included 54 pediatric patients with grade B-D SR-aGVHD after receiving allogeneic HSCT. The underlying reasons for allogeneic HSCT were hematologic malignancies (67%) and non-malignant disease (37%). The trial demonstrated an overall response rate of 70% (n = 38/54).

According to the National Comprehensive Cancer Network (NCCN) guidelines, treatment of SR-aGVHD involves consideration of several second-line agents. There is, however, no single standard approach. Options may include ruxolitinib, anti-thymocyte globulin, and extracorporeal photopheresis. Ryoncil has not yet been added to the NCCN guidelines.

POLICY:

Ryoncil (remestemcel-l-rknd) - Medical
1. Must be prescribed by or in consultation with an oncologist, hematologist, BMT specialist, or other qualified health professionals experienced in the management of Steroid Refractory acute Graft versus Host Disease (SR-aGVHD) **AND** 2. Patient must be ≥2 months to 17 years of age **AND** 3. Must have a diagnosis of Steroid Refractory acute Graft versus Host Disease (SR-aGVHD) following receipt of allogeneic hematopoietic stem cell transplantation (HSCT) **AND** 4. Must have Grade B–D aGvHD as defined using the modified Glucksberg grading system or the International Blood and Marrow Transplantation Registry (IBMTR). Objective documentation must be submitted confirming grade (severity) of disease (including but not limited to skin involvement [BSA], serum bilirubin levels, and stool volume [mL/day]) a. Grade III-IV (modified Glucksberg)/C-D (IBMTR) disease involving the skin, liver, or gastrointestinal (GI) tract **OR** b. Grade II (modified Glucksberg)/B (IBMTR) disease involving the liver or gastrointestinal (GI) tract with or without concomitant skin disease **AND** 5. Must have documentation of steroid refractory defined as progression within 3 days or no improvement within 7 days of consecutive treatment with 2 mg/kg/day methylprednisolone (or prednisone dose equivalent) 6. Must have a medical reason why Jakafi **AND** all NCCN Category 2A recommended alternative therapies for Steroid Refractory acute Graft versus Host Disease (SR-aGVHD) cannot be used (e.g., ECP, basiliximab, infliximab, ATG). a. A letter of medical necessity must be submitted confirming that all alternative therapies including Jakafi and NCCN category 2A alternative therapies are not appropriate or suitable *considering the specific organ involvement, severity of SR-aGVHD, prior treatment history, comorbidities, and the institutional experience*. **AND** 7. Baseline documentation of all organ involvement, including unaffected organs at the time of diagnosis, will be required. Incomplete documentation may result in an inability to evaluate the patient's eligibility for additional or repeat treatment. 8. Treatment Response Evaluation a. Response should be evaluated i. 28 days after the first dose for Initial Treatment ii. 56 days after Continued Therapy (if applicable) **AND** b. Objective documentation must be submitted confirming the patient's response to therapy (including but not limited to skin involvement [BSA], serum bilirubin levels, and stool volume [mL/day]) **AND** c. Response must be assessed across all organ systems that were documented as baseline and will be identified as one of the following: i. Partial or Mixed Response o Partial Response – defined as organ improvement of at least one stage without worsening of any other organ o Mixed response – defined as improvement in at least on evaluable organ stage with worsening in another ii. Complete Response - defined as a resolution of acute GVHD in all involved organs iii. No Response - defined as no change in any organ stage in any organ system and no improvement in organ stage. 9. Requirements for Continued or Additional (Recurrence) Treatment a. For Continued Treatment, the patient must have had a Partial or Mixed Response (as defined in 8.c.i.) to Initial Treatment **OR**

b. For Additional (Recurrence) Treatment, the patient must have achieved a Complete Response (as defined in 8.c.ii.) to treatment (Initial or Continued) **AND**
   i. The patient must have a return or worsening of SR-aGVHD symptoms consistent with the requirements in criteria 4 (above)
      a) Occurring more than 28 days after the first infusion of Initial Therapy **OR**
      b) Occurring more than 56 days after achieving Complete Response to continued therapy **AND**
   ii. The patient must not have initiated another systemic therapy for Steroid Refractory acute Graft versus Host Disease (SR-aGVHD)

c. No Response: Additional treatment will not be authorized for patients who had No Response to the initial treatment course.

10. Approved Dosage:
    a. Initial Treatment: 2×10^6 mesenchymal stromal cells (MSC)/kg body weight per intravenous infusion given *twice* a week for 4 consecutive weeks for a total of 8 infusions
    b. Continued or Additional (Recurrence) Treatment
       i. For Partial or Mixed Response: 2×10^6 mesenchymal stromal cells (MSC)/kg body weight per intravenous infusion given *once* weekly for an additional 4 weeks for a total of 4 additional infusions (12 infusions total)
       ii. For recurrence of SR-aGVHD after Complete Response: 2×10^6 mesenchymal stromal cells (MSC)/kg body weight per intravenous infusion given *twice* a week for an additional 4 consecutive weeks for a total of 8 additional infusions (16 infusions total)
11. Approval Timeframes:
    a. Initial Treatment: 4 weeks (28-days)
    b. Repeated Administration
       i. For Partial or Mixed Response: 4 weeks (28-days)
       ii. For recurrence of SR-aGVHD after Complete Response: 4 weeks (28-days)
    c. The approved dosage (10a,b) are provided per *lifetime*
12. Ryoncil will not be approved for uses beyond FDA approved indications including but not limiting to the treatment of chronic GVHD, non-SR-aGVHD, SR-aGVHD not associated with allogeneic HSCT, concomitant use with other systemic first-line or second-line SR-aGVHD therapies, adult patients with SR-aGVHD.

POLICY GUIDELINES:

1. Utilization Management are contract dependent. Refer to specific contract/benefit language for exclusions.
   a. Coverage criteria may be dependent on the contract renewal date.
   b. Coverage of drugs listed in this policy are contract dependent.
   c. Not all contracts/benefits allow coverage of healthcare professional administered drugs as part of their pharmacy benefit
   d. Not all contracts/benefits cover all medical infusible drugs.
2. This policy does not apply to Medicare Part D and D-SNP pharmacy benefits. The drugs in this policy may apply to all other lines of business including Medicare Advantage (Medicare Part B).
3. Clinical documentation must be submitted for each request (initial and recertification [if applicable]) unless otherwise specified (e.g., provider attestation required). Supporting documentation includes, but is not limited to, progress notes documenting previous treatments and treatment history, diagnostic testing, laboratory test results, genetic testing or biomarker results, imaging, and other objective or subjective measures of clinical benefit.
4. For members with Medicare Advantage, medications with a National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) will be covered pursuant to the criteria

outlined by the NCD and/or LCD. NCDs/LCDs for applicable medications can be found on the CMS website at https://www.cms.gov/medicare-coverage-database/search.aspx. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS permits a Medicare Advantage Organization (MAO) to establish its own coverage determinations in accordance with 42 CFR § 422.101(b)(6). Indications that have not been addressed by the applicable medication's LCD/NCD will be covered in accordance with criteria determined by the Health Plan. Step therapy requirements may be imposed in addition to LCD/NCD requirements.

5. All utilization management requirements outlined in this policy are compliant with applicable New York State insurance laws and regulations. Policies will be reviewed and updated as necessary to ensure ongoing compliance with all state and federally mandated coverage requirements
6. Prior authorization applies regardless of the site of administration (applies to both the inpatient and outpatient setting).
7. Unless otherwise indicated within drug specific criteria, the drugs listed in this policy are administered by a healthcare professional and therefore are covered under the medical benefit.
8. This policy is subject to ongoing revision. Newly marketed drugs and existing drugs with new indications may be subject to prior authorization until formal coverage criteria are established. Inclusion of a drug in this policy does not guarantee its current availability on the market, as some agents may be discontinued, withdrawn, or otherwise unavailable. As product status changes, drugs may be removed from the policy.
9. This policy is based on available evidence as of the last review date. Coverage determinations are subject to applicable plan documents, state and federal regulations, and individual patient circumstances. This policy does not constitute medical advice.
10. For commercial contracts, medical necessity determinations align with the Certificate of Coverage issued by the Health Plan, which states that covered services must be clinically appropriate and not primarily for the convenience of the member, the member's family, or the provider.
11. Manufacturers may either discontinue participation in, or may not participate in, the Medicaid Drug Rebate Program (MDRP). Under New York State Medicaid requirements, physician-administered drugs must be produced by manufacturers that participate in the MDRP. Products made by manufacturers that do not participate in the MDRP will not be covered under Medicaid Managed Care/HARP lines of business. Drug coverage will not be available for any product from a non-participating manufacturer. For a complete list of New/Reinstated & Terminated Labelers please visit: https://www.medicaid.gov/medicaid/prescriptiondrugs/medicaid-drug-rebate-program/newreinstated-terminated-labeler-information/index.html
12. The requested site of care may impact approval timeframe and is subject to review.
13. The following applies to all gene and cellular therapies unless otherwise specified within the drug-specific coverage criteria:
    a. Administration, Retreatment, and Treatment with Additional or Other Gene/Cellular Therapies
        i) One-Time Administration
            (1) Most gene and cellular therapies, whether autologous, allogeneic ("off-the-shelf"), or in vivo gene-transfer therapies, are designed and studied as one-time treatments.
            (2) Repeat dosing, reinfusion, or sequential therapy with other gene or cellular products has not been established as safe, effective, or clinically appropriate.
        ii) Retreatment/Repeat Administration
            (1) Retreatment with the same gene or cellular therapy product is considered experimental and investigational because:
                (a) Clinical trials evaluated these therapies as single-administration interventions
                (b) Safety, efficacy, and durability of a second administration have not been established

(c) Risks of immune activation, insertional mutagenesis, or vector immunity may be increased with repeat dosing

iii) Treatment with an Additional or Other Gene/Cellular Therapy
(1) Treatment with an additional or different gene or cellular therapy after prior exposure to any gene or cellular therapy is currently considered experimental and investigational as there is lack of evidence demonstrating the following (a-c):
(a) Anticipated clinical benefit beyond available standard therapies
(b) Safety of sequential administration
(c) Justification for selecting a second gene/cellular intervention after a prior one
(2) This includes, but is not limited to:
(a) Switching between CAR-T products (e.g., CD19 → CD19 or CD19 → BCMA)
(b) Switching between autologous and allogeneic cellular therapies
(c) Sequential use of CAR-T, TCR-T, NK-cell therapies, or other genetically engineered cell therapies
(d) Receiving a gene therapy after previous gene or cellular therapy exposure
(e) Receiving an in vivo gene therapy following any prior vector-based therapy

iv) Prior Gene/Cell Therapy Exposure
(1) An individual is generally not eligible for additional gene or cellular therapy if they have previously received:
(a) Any autologous cellular therapy (e.g., CAR-T, TCR-T, TIL),
(b) Any allogeneic genetically modified cellular therapy,
(c) Any in vivo gene therapy (e.g., AAV, lentiviral vector)
(d) Any ex vivo gene-modified cell product
(e) Are being considered for any other gene or cellular therapy without documented evidence supporting safety and anticipated benefit.

CODES:

Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. Codes may not be covered under all circumstances. Please read the policy and guideline statements carefully. Codes may not all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.
Code Key: Experimental/Investigational = (E/I). Not medically necessary/appropriate = (NMN).

HCPCS: J3490 Ryoncil

UPDATES:

Date	Revision
06/12/2026	Revised
06/01/2020	Revised
05/14/2026	P&T Committee Approval
11/19/2025	Revised
05/08/2025	P&T Committee Approval
05/08/2025	Policy Created & Implemented

REFERENCES:

1. Ryoncil Prescribing Information. January 2025
2. Kurtzberg J, 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 Graft-versus-Host Disease. Biol Blood Marrow Transplant. 2020 May;26(5):845-854. doi: 10.1016/j.bbmt.2020.01.018. Epub 2020 Feb 1. PMID: 32018062; PMCID: PMC8322819.
3. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Hematopoietic Cell Transplantation, v1.2025. https://www.nccn.org