

remestemcel-L-rknd (Ryoncil®)**Policy # 00933**

Original Effective Date: 07/01/2025

Current Effective Date: 07/01/2026

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Investigational or experimental services are not covered. This includes any drug, device, procedure, or service provided under the investigational arm of a clinical trial or clinical study. These services are excluded from coverage under benefits.

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 Company may consider remestemcel-L-rknd (Ryoncil®)[†] for the treatment of steroid refractory acute graft versus host disease (SR-aGvHD) to be **eligible for coverage**.^{**}

Patient Selection Criteria

Coverage eligibility for remestemcel-L-rknd (Ryoncil) will be considered when the following criteria are met:

Initial

- Patient has undergone allogeneic hematopoietic cell transplantation (HCT); AND
- Patient has a diagnosis of acute graft versus host disease (aGvHD); AND
- Patient is greater than or equal to 2 months of age and less than 18 years of age; AND
- Patient's disease is steroid refractory (SR) as defined by progression within 3 days or no improvement within 7 days of consecutive treatment with 2 mg/kg/day methylprednisolone or equivalent; AND
- Patient has been diagnosed with one of the following (See Policy Guidelines section for IBMTR Severity Index Criteria):
 - Grade C or D aGvHD according to the International Blood and Marrow Transplantation Registry (IBMTR) Severity Index Criteria with symptoms involving the skin, liver, or GI tract; **OR**
 - Grade B aGvHD according to the IBMTR Severity Index Criteria with symptoms involving the liver or GI tract; AND

*(Note: These specific patient selection criteria are additional Company requirements for coverage eligibility and will be denied as not medically necessary** if not met.)*

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- If the patient is greater than or equal to 12 years of age, patient has tried and failed (e.g., intolerance or inadequate response) ruxolitinib (Jakafi®)† unless there is clinical evidence or patient history that suggests the use of ruxolitinib will be ineffective or cause an adverse reaction to the patient; AND
(Note: This specific patient selection criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met.)
- Dose will not exceed 2×10^6 mesenchymal stromal cells (MSCs)/kg given twice weekly for 4 consecutive weeks.

Continuation

- Patient has a previous approval for Ryoncil; AND
- Patient has not received more than 16 infusions of Ryoncil; AND
- Patient meets ONE of the following:
 - Patient has experienced a partial or mixed response on therapy with Ryoncil and will receive Ryoncil once weekly for 4 additional weeks (4 infusions total); OR
 - Patient's disease has recurred after a complete response and will receive Ryoncil twice weekly for 4 additional weeks (8 infusions total).

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of remestemcel-L-rknd (Ryoncil) when the patient does NOT have Grade C or D aGvHD with symptoms involving the skin, liver, or GI tract, or Grade B aGvHD with symptoms involving the liver or GI tract to be **not medically necessary**.**

Based on review of available data, the Company considers the use of remestemcel-L-rknd (Ryoncil) when the patient is greater than or equal to 12 years of age and has not tried and failed ruxolitinib (Jakafi) 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 Company considers the use of remestemcel-L-rknd (Ryoncil) when patient selection criteria are not met (except those listed above as **not medically necessary****) to be **investigational**.*

Policy Guidelines

International Bone Marrow Transplant Registry (IBMTR) grading system

Grade	Characteristics
Grade A	Stage 1 skin involvement alone (maculopapular rash over < 25% of the body) with no liver or gastrointestinal involvement
Grade B	Stage 2 skin involvement; Stage 1 to 2 gut or liver involvement
Grade C	Stage 3 involvement of any organ system (generalized erythroderma; bilirubin 6.1 to 15.0 mg/dL; diarrhea 1500 to 2000 mL/day)
Grade D	Stage 4 involvement of any organ system (generalized erythroderma with bullous formation; bilirubin > 15 mg/dL; diarrhea > 2000 mL/day or pain or ileus)

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Background/Overview

Ryoncil is a novel therapy composed of culture-expanded mesenchymal stromal cells (MSCs) derived from the bone marrow of an unrelated donor and approved for the treatment of steroid-refractory acute graft versus host disease (aGvHD) in pediatric patients. This product has immunomodulatory properties that counteract cytokine storms by downregulating the production of pro-inflammatory cytokines, increasing the production of anti-inflammatory cytokines and recruiting naturally occurring anti-inflammatory cells to involved tissues. It is administered as a twice weekly intravenous infusion at a dose of 2×10^6 MSCs/kg for 4 consecutive weeks. After 28 days from the first dose, further treatment can be administered (up to a maximum lifetime dose of 16 infusions) depending on the patient's response.

Graft-versus-host disease (GvHD) is a condition that may occur after an allogeneic hematopoietic cell transplant (HCT) in which the transplanted cells from the donor induce an immune response in the recipient, encouraging the host's immune system to attack and reject the newly transplanted cells. GVHD is categorized as either acute (aGvHD) or chronic (cGvHD) with differentiation established by consensus criteria from the National Institutes of Health (NIH). Acute GvHD classically presents in the early post-transplant period, with initial signs and symptoms often occurring around the time of white blood cell engraftment. Common manifestations include skin rash, gastrointestinal distress, and liver abnormalities. aGvHD occurs in 30-70% of patients who receive an allogeneic HCT, though its incidence has decreased due to improved utilization of prophylactic therapies. Steroid-refractory (SR)-aGvHD may occur in up to 50% of patients with aGVHD and is associated with mortality as high as 80%. Treatment of aGvHD depends on the severity of disease and organs involved, but begins with some form of local or systemic corticosteroids. Therapeutic response is assessed after 5-7 days and patients with disease progression or limited response are classified as steroid refractory (SR). For those with SR-aGvHD, ruxolitinib (Jakafi) is FDA approved in patients ≥ 12 years of age. If this is ineffective, other immunomodulatory agents may be tried, but the preferred treatment varies among institutions and is influenced by availability, cost, and patient preference.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Ryoncil was approved in December 2024 for the treatment of steroid-refractory acute graft versus host disease in pediatric patients ≥ 2 months of age.

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 Ryoncil was evaluated in a multicenter, prospective, single-arm study (MSB-GVHD 001). The study enrolled pediatric patients with SR-GvHD Grade B to D (excluding Grade B skin alone) as per International Blood and Marrow Transplantation Registry Severity Index Criteria

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(IBMTR) after receiving allogeneic hematopoietic cell transplantation (HCT). SR-aGvHD was defined as aGvHD that progressed within 3 days or did not improve within 7 consecutive days of treatment with methylprednisolone 2 mg/kg/day or equivalent. Patients who received a second line therapy for aGvHD prior to screening were excluded.

Ryoncil was administered by intravenous infusion at a dosage of 2×10^6 MSCs/kg twice a week for four consecutive weeks, for a total of eight infusions. Patients with partial or mixed response at Day 28 received additional infusions of Ryoncil 2×10^6 MSCs/kg once a week for an additional four consecutive weeks. Patients with complete response at Day 28 who experienced recurrence of aGvHD received infusions of Ryoncil 2×10^6 MSCs/kg twice a week for an additional four consecutive weeks.

A total of 55 patients were enrolled, and 54 were treated with Ryoncil. Among the treated patients (n = 54), the demographic characteristics were as follows: median age was 7 years (range: 7 months to 17 years); 36% were females; 56% were White, 19% reported “other” race, 15% were Black, 6% were Asian, 6% American Indian or Alaska Native, 33% were Hispanic and 65% were non-Hispanic. Among enrolled patients, hematologic malignancies (67%) and non-malignant diseases (33%) were the underlying reasons for allogeneic HCT. SR-GvHD severity was as follows at baseline: Grade B (11%), Grade C (43%), Grade D (46%). Organ involvement at baseline were as follows: skin alone (26%), lower gastrointestinal tract only (39%), multi-organ involvement (35%). The median duration of prior corticosteroid treatment at baseline was 8 days (range: 2 to 46 days).

The main efficacy outcome measures were Day-28 overall response rate (complete response rate and partial response rate) and the duration of response. Of the 54 treated patients, 38 (70%) responded with 16 (30%) achieving a complete response and 22 (41%) achieving a partial response. The duration of response was an average of 54 days from day 28 with a range of 7 to 159+ days.

References

1. Ryoncil [package insert]. Mesoblast, Inc. New York, NY. Updated April 2025.
2. Ryoncil (remestemcel-L-rknd). New Drug Review. IPD Analytics. Updated January 2025.
3. Chao, NJ. Clinical manifestations, diagnosis, and grading of acute graft-versus-host disease. UpToDate. Updated April 2025.
4. Ziser, R. Treatment of acute graft-versus-host disease. UpToDate. Updated May 2025.

Policy History

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06/05/2025 Medical Policy Committee review

06/11/2025 Medical Policy Implementation Committee approval. New policy.

10/01/2025 Coding update.

06/04/2026 Medical Policy Committee review.

06/10/2026 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2027

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Coding

The five character codes included in the Louisiana Blue Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2025 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.

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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	No codes
HCPCS	J3402 Delete codes effective 07/01/2026: C9399, J3590
ICD-10 Diagnosis	All Related Diagnoses

*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);

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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 BCBSLA 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 Company 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.

NOTICE: If an authorization for an ongoing course of treatment has been provided to a member and the member changes from one health plan to another health plan (e.g., a member moves from carrier A to Louisiana Blue), Louisiana Blue may honor the previous health plan’s authorization for the same service under the same type of in-network benefit for a 90-day transition period. Documentation of the authorization for the ongoing course of treatment from the previous health plan must be provided to us by the member or their provider and the services provided for the course of treatment must otherwise be a covered service under the Louisiana Blue health plan. This provision does not apply to medications covered under the plan’s pharmacy benefit.