09-J5000-14

Original Effective Date: 03/15/25

Reviewed: 01/14/26

Revised: 06/01/26

Subject: Remestemcel-l-rknd (Ryoncil) Infusion

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Remestemcel-L-rknd (Ryoncil) is FDA-approved for the treatment of steroid-refractory acute graft-versus-host disease (SR-aGvHD) in pediatric patients greater than or equal to 2 months of age. It contains mesenchymal stromal cells (MSC) from the bone marrow of healthy human adult donors. MSCs inhibit T-cell activation which have a role in the inflammatory response and organ damage associated with acute graft-versus-host disease (aGvHD).

The efficacy of remestemcel-l-rknd was evaluated in a single-arm study in pediatric patients with SR-aGvHD after receiving allogeneic hematopoietic stem cell transplantation (HSCT). SR-aGvHD was defined as progression within 3 days or no improvement within 7 consecutive days of treatment with methylprednisolone 2 mg/kg/day or equivalent. Patients were included with Grade B to D (excluding Grade B skin alone) SR-aGvHD as defined by the International Blood and Marrow Transplantation Registry (IBMTR) Severity Index Criteria. Patients were excluded if they received a second line therapy for aGvHD prior to screening.

There were 54 patients treated with remestemcel-l-rknd which included patients age 7 to 17 years old. Patients' organ involvement included skin alone (26%), lower gastrointestinal tract only (39%), and multi-organ involvement (35%). Disease severity at baseline included Grade B (11%), Grade C (43%), and Grade D (46%) according to the IBMTR Severity Index Criteria. Patients received a dose of 2 x 10^6 MSCs/kg twice a week (at least 3 days apart) for four consecutive weeks (8 infusions total). If the patient had a partial or mixed response at Day-28, they could receive an additional dose of 2 x 10^6 MSCs/kg once a week for four consecutive weeks. Patients who experienced a recurrence of aGvHD after an initial complete response at Day-28 could receive a dose of 2 x 10^6 MSCs/kg twice a week for an additional four consecutive weeks (8 infusions following disease recurrence). The main efficacy outcome measures were the Day-28 response rate including both complete and partial response, and the duration of response. The overall response rate at day 28 included 38 patients (70%, 95% CI (56.4, 82)) for a median duration of 54 days (7, 159+). A complete response occurred in 16 patients (30%, 95% CI (18, 43.6)) and was defined as a resolution of aGvHD in all involved organs as per the IBMTR grading system. A partial response occurred in 22 patients (41%, 95% CI 27.6, 55)) and was defined as organ improvement of at least one stage without worsening of any other organ. The most common adverse reactions occurring in greater than 20% of patients included viral and bacterial infections, pyrexia,

gamma-glutamyl transferase increase, thrombocytopenia, hemorrhage, edema, abdominal pain, and hypertension.

POSITION STATEMENT:

Drug Waste Reduction: Additional medical necessity criteria for dose optimization may apply depending on the requested dose and member's benefit. Refer to Medical Coverage Guideline Drug Waste Reduction, 09-J5000-54.

I. Initiation of remestemcel-l-rknd (Ryoncil) **meets the definition of medical necessity** for the following indications when ALL of the associated criteria are met:
   1. Steroid refractory acute graft-versus-host disease (SRaGVHD) and **ALL** of the following– documentation must be submitted:
      a. The member is diagnosed with aGVHD following an allogeneic hematopoietic stem cell transplant
      b. Member's disease severity is classified as Grade B, C, or D according to the International Blood and Marrow Transplantation Registry (IBMTR) Severity Index Criteria
      c. Member had an inadequate response to methylprednisolone 2 mg/kg/day or equivalent defined as disease progression within 3 days of treatment or no improvement within 7 consecutive days of treatment
      d. Member is less than 18 years of age
   2. Remestemcel-l-rknd is prescribed by or in consultation with an oncologist, hematologist, or transplant specialist
   3. Dosage does not exceed 2 x 10^6 MSC/kg twice a week (at least 3 days apart) for four consecutive weeks (8 infusions total)

Approval duration: 1 month

II. Continuation of remestemcel-l-rknd (Ryoncil) **meets the definition of medical necessity** when **ALL** of the following criteria are met:
   1. An authorization or reauthorization for remestemcel-l-rknd has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of aGVHD, OR the member has previously met **ALL** indication-specific criteria.
   2. The member has **ONE** of the following responses following the initial 8 doses of remestemcel-l-rknd– documentation must be submitted:
      a. Partial response (i.e., organ improvement of at least one stage per the International Blood and Marrow Transplantation Registry (IBMTR) Severity Index Criteria without worsening in any other organ)
      b. Mixed response (i.e., improvement of at least one organ with worsening in another organ per the IBMTR Severity Index Criteria)
      c. Recurrence of aGvHD following complete response (i.e., disease recurrence following a resolution of aGvHD in all involved organs)
   3. Remestemcel-l-rknd is prescribed by or in consultation with an oncologist, hematologist, or transplant specialist
   4. Dosage does not exceed **ONE** of the following and the member has not received more than 16 infusions total:

a. Partial or mixed response: 2 x 10^6 MSC/kg once a week for four consecutive weeks (4 infusions total).

b. Disease recurrence following complete response: 2 x 10^6 MSC/kg twice a week (at least 3 days apart) for four consecutive weeks (8 infusions total).

Approval duration: 1 month

DOSAGE/ADMINISTRATION:

Remestemcel-L-rknd suspension for intravenous infusion is indicated for the treatment of steroid-refractory acute graft versus host disease in pediatric patients 2 months of age and older. It is dosed as 2 x10^6 mesenchymal stromal cell (MSC) per kilogram of body weight given twice per week for 4 consecutive weeks. Infuse at least 3 days apart.

Assess the response 28 ± 2 days after the first dose and administer further treatment as appropriate as described below:

Recommended Treatment Based on Day 28 Response	
Response	**Recommendation**
Complete Response (CR)	No further treatment
Partial or Mixed Response	Repeat administration once a week for additional 4 weeks (4 infusions total)
No Response	Consider alternative treatments
Recurrence of GVHD after CR	Repeat administration twice a week for an additional 4 consecutive weeks (8 infusions total)

PRECAUTIONS:

Boxed Warning - none

Contraindications

Known hypersensitivity to dimethyl sulfoxide (DMSO) or Porcine and Bovine proteins.

Precautions/Warnings

- Hypersensitivity/Acute Infusion reactions: Monitor for hypersensitivity reactions during infusion and premedicate with corticosteroids and antihistamines.
- Transmission of infectious agents: may transmit infectious agents.
- Ectopic tissue formation: ectopic tissue formation may occur following treatment.

Dosage Forms

Available as a 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.

BILLING/CODING INFORMATION:

HCPCS Coding

J3402	Injection, remestemcel-l-rknd, per therapeutic dose

ICD-10 Diagnosis Codes That Support Medical Necessity

D89.810	Acute graft-versus-host disease

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

International Blood and Marrow Transplantation Registry (IBMTR) Severity Index Criteria

Grade	Skin	Liver	Lower GI	Upper GI
A	1	0	0	0
B	2	1-2	1-2	1
C	3	3	3	N/A
D	4	4	4	N/A

Modified Glucksberg Criteria

Stage	Skin	Liver	Lower GI	Upper GI
0	No rash	Bilirubin < 2 mg/dL	Diarrhea < 500 mL/day	No persistent nausea; no evidence of GVHD in stomach or duodenum
1	< 25%	Bilirubin 2-3 mg/dL	Diarrhea > 500 mL/day or persistent nausea	Persistent nausea with histologic evidence of GVHD in stomach or duodenum
2	25 – 50%	Bilirubin 3.1-6 mg/dL	Diarrhea > 1,000 mL/day	N/A
3	50%	Bilirubin 6.1-15 mg/dL	Diarrhea > 1,500 mL/day	N/A
4	Erythroderma with bullous formation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus	N/A

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 01/14/26.

GUIDELINE UPDATE INFORMATION:

03/15/25	New Medical Coverage Guideline.
10/01/25	Revision: Added HCPCS code J3402 and removed code J3590.
02/15/26	Review and revision to guideline; including update to references.
06/01/26	Revision: Added Drug Waste Reduction statement to the Position Statement.