Medical Policy

Subject:	Allogeneic Bone Marrow-Derived Mesenchymal Stromal Cell Therapy		
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Description/Scope

This document addresses allogeneic bone marrow-derived mesenchymal stromal cell (MSC) therapy, which has been studied as a treatment for steroid-refractory acute graft versus host disease (SR-aGvHD). SR-aGvHD is a serious condition which may develop as a consequence of hematopoietic stem cell transplantation (HSCT). Remestemcel-L-rknd (Ryoncil®) is the first MSC therapy approved by the U.S. Food and Drug Administration (FDA) and is indicated for the treatment of steroid-refractory acute graft versus host disease (SR-aGvHD) in pediatric individuals 2 months of age and older. In Ryoncil therapy, mesenchymal stromal cells (MSCs) isolated from the bone marrow of healthy adult donors are infused into an individual with SR-aGvHD to combat overactivity of the immune system and accompanying inflammation and tissue damage.

Note: Please see the following related document for additional information:

- TRANS.00035 Therapeutic use of Stem Cells, Blood and Bone Marrow Products

Position Statement

Medically Necessary:

An *initial course of treatment (twice per week for four weeks)* with remestemcel-L-rknd (Ryoncil) is considered **medically necessary** in individuals when **all** of the following criteria are met:

A. Diagnosed with SR-aGvHD grade B to D (excluding skin-only grade B) after receiving allogeneic hematopoietic stem cell transplantation (HSCT); **and**
B. Aged 2 months to 17 years; **and**
C. Have no known incidence of **any** of the following:
    1. Active treatment for a solid tumor malignancy; **or**
    2. Evidence of diffuse alveolar hemorrhage or other active pulmonary disease; **or**
    3. Evidence of severe hepatic veno-occlusive disease or sinusoidal obstruction; **or**
    4. HSCT for a solid tumor disease; **or**
    5. Hypersensitivity to dimethyl sulfoxide (DMSO) or porcine and bovine proteins; **or**
    6. Prior treatment with MSCs, including remestemcel-L-rknd.

A *repeat course of treatment* with remestemcel-L-rknd (Ryoncil) is considered **medically necessary** when the following criteria have been met:

A. Partial or mixed response to the initial treatment *(repeat once per week for four weeks)*; **or**
B. Recurrence of SR-aGvHD after complete response *(repeat twice per week for four weeks)*.

Not Medically Necessary:

Repeat treatment with remestemcel-L-rknd (Ryoncil) is considered **not medically necessary** when the initial treatment has resulted in either of the following:

A. Complete response; **or**
B. No response.

Investigational and Not Medically Necessary:

Initial or repeat treatment with remestemcel-L-rknd (Ryoncil) is considered **investigational and not medically necessary** when any of the medically necessary criteria above are not met.

Rationale

Ryoncil is an allogeneic bone marrow-derived MSC therapy indicated for the treatment of SR-aGvHD. It is comprised of culture-expanded MSCs isolated from the bone marrow of healthy adult human donors. Ryoncil is administered intravenously at a dosage of 2×10^6 MSC/kg body weight per infusion given twice per week for 4 consecutive weeks. Response to treatment is assessed 28 days after the first dose. If the response is only partial, Ryoncil administration may be continued once a week for an additional 4 weeks.

This product has been evaluated in one published study, a phase 3, single-arm, multicenter, prospective study of remestemcel-L, for the treatment of pediatric individuals who failed to respond to steroid treatment for aGvHD (Kurtzberg, 2020). This study (NCT02336230) was designed to evaluate the efficacy and safety of remestemcel-L in children with primary SR-aGVHD in the absence of additional immunosuppressive therapy for aGVHD. A total of 54 children aged 2 months to 17 years with primary SR-aGVHD who were naive to other immunosuppressant therapies for aGVHD were treated with remestemcel-L. Assessments of aGVHD were performed at baseline and then weekly from day 14 after the first MSC infusion until day 100. Severity of aGVHD was evaluated using the Center for International Blood and Marrow Transplant Research (CIBMTR) grading criteria (Rowlings, 1997). Remestemcel-L therapy produced an overall response rate (complete response + partial response) at day 28 of 70.4% which was a significant improvement compared with historical age- and disease-severity-adjusted published findings for standard of care alone (70.4% versus 45%, p=0.003). The overall response rate of 70.4% was sustained through day 100, and the complete response rate increased from 29.6% at day 28 to 44.4% at day 100. Overall survival was 74.1% at day 100 and 68.5% at day 180.

The safety of remestemcel-L was also evaluated. Three participants experienced acute infusion reactions. A total of 16 adverse events in 9 participants (17%) were assessed as possibly related to remestemcel-L treatment. Ten of these events were considered non-serious and expected in this population; 6 events were serious, which included skin GvHD, adenovirus infection, BK virus infection, hemolytic uremic syndrome, hypermetabolism, and somnolence. The potential for ectopic tissue formation is also a concern, due to the ability of MSCs to differentiate into other tissues such as fat, cartilage, and bone. In this study, there was no evidence suggestive of ectopic tissue formation in any participant based on computed tomography scans performed at day 180.

Key inclusion criteria for the trial (NCT02336230) included the following:

- Individuals between the ages of 2 months and 17 years.
- Diagnosis of aGVHD following allogeneic HSCT that has failed to respond to treatment with systemic corticosteroid therapy.

- Participants with Grades C and D aGVHD involving the skin, liver or gastrointestinal (GI) tract or Grade B aGVHD involving the liver or GI tract, with or without concomitant skin disease.

On December 18, 2024, the U.S. Food and Drug Administration (FDA) approved remestemcel-L-rknd (Ryoncil) for the treatment of SR-aGVHD in pediatric individuals 2 months and older. Ryoncil is the first FDA-approved MSC therapy and the only approved therapy for pediatric individuals with SR-aGVHD. According to the package insert, the recommended dosage is 2×10^6 MSC/kg body weight per intravenous infusion given twice per week for 4 consecutive weeks. It is recommended that the response to treatment be assessed on day 28 after the first dose. A complete response is defined as resolution of aGVHD in all involved organs. Further treatment consisting of repeat administration of Ryoncil once a week for an additional 4 weeks may be administered if there is a partial or mixed response. Partial response is defined as organ improvement of at least one stage without worsening in any other organ; mixed response is defined as improvement of at least one organ with worsening in another organ as per CIBMTR grading criteria. Repeat administration of Ryoncil twice a week for an additional 4 consecutive weeks may also be considered if there is a recurrence of GvHD after a complete response.

Ryoncil is contraindicated in individuals with known hypersensitivity to dimethyl sulfoxide (DMSO) or porcine and bovine proteins. The following warnings and precautions for Ryoncil were listed in the product insert:

- Hypersensitivity/Acute Infusion reactions: Monitor for hypersensitivity reactions during infusion and premedicate with corticosteroids and antihistamines. (5.1)
- Transmission of Infectious Agents: RYONCIL may transmit infectious agents. (5.2)
- Ectopic Tissue Formation: Ectopic tissue formation may occur following treatment with RYONCIL. (5.3)

In summary, despite the promise of HSCT as a curative treatment for many serious disorders, there is high morbidity and mortality among children who develop SR-aGVHD following HSCT. This consequence is due in large part to the lack of effective treatment options for these individuals. The available peer-reviewed literature on the use of Ryoncil in children is limited to one report (Kurtzberg, 2020). However, given the serious morbidity and mortality of SR-aGvHD, this limited evidence supports the medical necessity of Ryoncil in appropriately selected individuals. Long term data on both safety and effectiveness of treatment with Ryoncil are lacking (the longest follow-up in the study was 180 days), including the possibility of ectopic tissue formation.

Background/Overview

According to data from the CIBMTR, approximately 4500 children undergo allogeneic bone marrow transplantation in the United States each year. About 50% of these cases develop aGvHD and almost half of those do not respond to steroids, resulting in about 1125 children per year in the US with SR-aGvHD.

Acute GVHD occurs when immune cells transplanted from a non-identical donor (graft) into the recipient (host) recognize the host cells as foreign and attack the host tissue (Zeiser, 2017). Symptoms develop within weeks or months of a transplant, and include skin rashes, gastrointestinal issues, and liver dysfunction. First-line therapy for aGVHD is treatment with glucocorticoids (steroids). However, if the disease progresses after 3 days of high-dose steroids or the individual does not improve after 7 days of treatment, the disease is said to be steroid-refractory. SR-aGVHD following HSCT is associated with poor clinical outcomes. Individuals with this condition have a high risk of mortality due to the potential for severe organ damage and infection. Studies show a mortality rate of approximately 70% for individuals with SR-aGvHD (Holtan, 2022).

The second-line treatment for SR-aGvHD is the Janus kinase 2 (JAK2) inhibitor ruxolitinib (Malard, 2023). However, ruxolitinib is only FDA-approved to treat adults and children 12 years of age and older with SR-aGvHD. Currently, there are no approved therapies specifically indicated for use in SR-aGvHD in children under the age of 12 years, a population with high unmet need and poor prognosis.

MSCs are multipotent cells found in various tissues throughout the body, including bone marrow, adipose tissue, and umbilical cord blood. They can differentiate into multiple cell types and have immunosuppressive effects which can help reduce inflammation and promote tissue repair (Wu, 2020). MSCs can respond to injury and infection by secreting and recruiting biological factors, and they have the ability to migrate to sites of injury or disease where they can exert their therapeutic effects. Due to their immunomodulatory and regenerative effects, MSC-based cellular therapy is being investigated for variety of pathological conditions including bone fracture, cancer, autoimmune diseases and transplantation.

Definitions

Allogeneic: Tissue or cells taken from different individuals from the same species.

CIBMTR grading criteria: A system used to assess the severity of aGVHD based on involvement of individual organs.

	Skin involvement			**Liver involvement**			**Gastrointestinal involvement**	
	Stage			Stage			Stage	
Grade		Extent of rash			Total bilirubin (mmol/l)			Volume of diarrhea (ml/d)
A	1	< 25%		0	< 34		0	< 500
B	2	25–50%	or	1–2	34–102	or	1–2	550–1500
C	3	> 50%	or	3	103–255	or	3	> 1500
D	4	Bullae	or	4	> 255	or	4	Severe pain and ileus

Complete response to treatment: Resolution of aGvHD in all involved organs as per CIBMTR grading system.

Hematopoietic stem cell transplantation (HSCT): A medical procedure that involves replacing damaged or diseased blood-forming cells with healthy stem cells.

Mixed response to treatment: Improvement of at least one organ with worsening in another organ as per CIBMTR grading criteria.

Partial response to treatment: Organ improvement of at least one stage without worsening of any other organ as per CIBMTR grading system.

Steroid-refractory acute graft versus host disease (SR-aGvHD): A condition that can occur after HSCT when the body's immune system attacks the new bone marrow cells (graft) and causes severe inflammation and organ damage, despite treatment with high doses of corticosteroids. Failure to respond to steroid therapy is defined as any Grades B to D (CIBMTR criteria) aGVHD that shows progression within 3 days or no improvement within 7 days of daily treatment with 2 mg/kg/day of methylprednisolone or equivalent.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

HCPCS

C9399	Unclassified drugs or biologicals [when specified as remestemcel-L-rknd (Ryoncil)]
J3490	Unclassified drugs [when specified as remestemcel-L-rknd (Ryoncil)]
J3590	Unclassified biologics [when specified as remestemcel-L-rknd (Ryoncil)]

ICD-10 Diagnosis

D89.810-D89.813	Graft-versus-host disease
T86.00-T86.09	Complications of bone marrow transplant
T86.5	Complications of stem cell transplant

When services are Investigational and Not Medically Necessary:
For the procedure codes listed above when criteria are not met or for all other diagnoses not listed.

References

Peer Reviewed Publications:

1. Holtan SG, Yu J, Paranagama D, et al. Disease progression, hospital readmissions, and clinical outcomes for patients with steroid-refractory acute graft-versus-host disease: a multicenter, retrospective study. Bone Marrow Transpl. 2022; 57:1399–1404.
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 graft-versus-host disease. Blood Bone Marrow Transpl. 2020; 26(5):845-854.
3. Malard F, Holler E, Sandmaier BM, et al. Acute graft-versus-host disease. Nat Rev Dis Primers. 2023; 9(1):27.
4. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. British Journal of Haematol. 1997; 97:855–864.
5. Wu X, Jiang J, Gu Z, et al. Mesenchymal stromal cell therapies: immunomodulatory properties and clinical progress. Stem Cell Res Ther. 2020; 11(1):345.
6. Zeiser R, Blazar BR. Acute graft-versus-host disease biology, prevention and therapy. N Engl J Med. 2017; 377(22):2167–2179.

Government Agency, Medical Society, and Other Authoritative Publications:

1. Center for International Blood and Marrow Transplant Research. Summary slides & reports. Available at: https://cibmtr.org/CIBMTR/Resources/Summary-Slides-Reports. Accessed on February 28, 2025.
2. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Available at: https://clinicaltrials.gov/ct2/home. Accessed on March 4, 2025.

- A Prospective Study of Remestemcel-L, Ex-vivo Cultured Adult Human Mesenchymal Stromal Cells, for the Treatment of Pediatric Participants Who Have Failed to Respond to Steroid Treatment for Acute Graft-Versus-Host Disease (aGVHD). NCT02336230.

3. U.S. Food and Drug Administration. RYONCIL® highlights of prescribing information. December 2024. Available at: https://www.fda.gov/media/184603/download. Accessed on March 4, 2025.

Websites for Additional Information

1. Leukemia & Lymphoma Society. Graft-versus-host-disease. Available at: https://www.lls.org/treatment/types-treatment/stem-cell-transplantation/graft-versus-host-disease. Accessed March 3, 2025.
2. U.S. National Library of Medicine. Graft-versus-host disease. Last reviewed June 17, 2024. Available at: https://medlineplus.gov/ency/article/001309.htm. Accessed March 4, 2025.

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Remestemcel-L-rknd
Ryoncil

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
New	05/08/2025	Medical Policy & Technology Assessment Committee (MPTAC) review. Initial document development.