Molina Clinical Policy
Ryoncil (remestemcel-L-rknd) Policy No. 467

Last Approval: 02/12/2025
Next Review Due By: February 2026

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

This policy reviews the use of Ryoncil (remestemcel-L) for the treatment for steroid-refractory, acute graft verse host disease (SR-aGvHD). Acute graft verse host disease (aGvHD) occurs after allogeneic hematopoietic cell transplantation, when grafted immune cells react to native host cells leading to inflammation and tissue destruction. If this condition occurs, it typically does so within 100 days of transplant and includes one or more symptoms such as a maculopapular rash, diarrhea, abdominal cramps and/or rising bilirubin.

Acute GVHD is defined as the presence of skin rash and/or persistent nausea, vomiting, and/or diarrhea and/or cholestasis presenting in a context in which aGVHD is likely to occur and where other etiologies such as drug rash, enteric infection, or hepatotoxic syndromes are unlikely or have been ruled out (NCT02336230). The severity of GvHD depends on the donor recipient match, the type of conditioning and prophylaxis. The severity of GvHD is communicated clinically using the grading system defined by the International Bone Marrow Transplant Registry Severity Index (see supplemental information for details).

Treatment is a function of the severity or grade of the GvHD. When skin only is involved, topical steroids can be used. When the gastrointestinal (GI) tract is involved, oral, non-absorbable steroids are used in the treatment regimen. The balance to strike in treating this condition is maintaining the graft verse tumor effect while minimizing graft verse host disease. Significant GvHD can lead to transplant failure or mortality. Elgaz et al. (2019) estimated 35-60% of patients are affected by GvHD and mortality rates can be as high as 90% (Kurtzberg 2020). If there is progression within three days of steroid treatment or no improvement after 7 days of treatment, the disease is classified as steroid refractory and additional agents such as Ruxolitinib are considered. Ruxolitinib is a jak stat inhibitor that reduces inflammation. It is indicated only for those 12 years of age and older. A gap in therapeutic options exist for the treatment of GvHD in the younger pediatric population.

Ryoncil is an allogenic mesenchymal stem cell therapy that received FDA approval for the treatment of SR-aGvHD in pediatric patients older than 2 months, helping to fill the gap in therapeutic options for this young age group. The mechanism of Ryoncil is not perfectly understood but is believed to involve the induction of regulatory T-cells that help moderate immune response.

COVERAGE POLICY

Ryoncil (Remestemcel-L) may be **considered medically necessary** when ALL the following criteria are met:

1. Member is ≥ 2 months of age but ≤ 17 years of age
2. Member is diagnosed with Grade B-D acute GvHD requiring corticosteroid systemic therapy. The member may have Grade C or D aGvHD involving the skin, liver, and/or GI tract or may have Grade B aGvHD involving the liver and/or GI tract, with or without concomitant skin disease. ([International Bone Marrow Transplant Registry (IBMTR) grading])

3. Member does not have Grade B aGvHD with skin-only involvement

4. A member may be considered to have GI Grade B aGvHD with persistent, low stool-volume diarrhea & absence of nausea or vomiting if
    a. other causes of diarrhea have been ruled out (eg, Clostridium difficile, adenovirus or cytomegalovirus [CMV] infection, or oral magnesium administration), and if
    b. the low stool volume reflected the effects of fasting, narcotics, or antidiarrheal medications.
    (** low stool volume defined by volume < 500 mL/kg/day for members >50 kg or <30 mL/kg/day for members ≤50 kg)

5. Member has failed to respond to steroid treatment, with failure to respond defined as any Grade B-D aGVHD that shows progression within 3 days, or no improvement within 7 days of consecutive treatment with 2 mg/kg/day methylprednisolone or equivalent (NCCN 2024)

6. Member must have adequate renal function (defined by a calculated creatinine clearance of >30 mL/min per 1.73 m^2 (for members 1year – 17 years of age, creatinine clearance is calculated using the Bedside Schwartz equation: Glomerular filtration rate (GFR, in mL/min per 1.73 m^2) = (0.413 * height [cm])/serum creatinine (mg/dL) For participants younger than 1 year of age, renal function is determined using the Schwartz equation adjusted for this age group: Creatinine clearance (mL/min per 1.73 m^2= (height [cm] x 0.45)/ (serum creatinine [mg/dL])

7. Member has a minimum Karnofsky/Lansky Performance Level of at least 30 prior to starting therapy

8. Member does not have evidence of diffuse alveolar hemorrhage or other active pulmonary disease, which is likely to require more than 2L of oxygen via face mask, or an estimated fractional inspired oxygen concentration (FiO2) of 28% via other delivery methods in order to sustain an O2 saturation of 92%

9. Member does not have any underlying or current medical or psychiatric condition that, in the opinion of the provider, would interfere with the evaluation of the member including but not limited to uncontrolled infection, heart failure, or pulmonary hypertension

10. Member has not received a HSCT transplant for a solid tumor disease or currently being treated for a solid tumor malignancy

11. Member does not have evidence of severe hepatic VOD (hepatic veno-occlusive disease) requiring treatment or sinusoidal obstruction

12. Member has not had positive laboratory test results indicating infection with the human immunodeficiency virus (HIV) at any time and/or active hepatitis B or C virus infection within 3 months prior to planned remestemcel therapy

13. Member does not show evidence of encephalopathy, as defined by a change in mental status since the onset of aGvHD

14. Member is not pregnant, lactating, or planning a pregnancy

15. Member agrees to use adequate contraception during treatment

16. Member does not have a known hypersensitivity to dimethyl sulfoxide (DMSO) or to murine, porcine, or bovine proteins

QUANTITY LIMITATIONS: Recommended dosage of RYONCIL is 2 × 10^6 MSC/kg body weight per intravenous infusion given twice per week for 4 consecutive weeks. Infusions should be administered at least 3 days apart.

CONTINUATION OF THERAPY: Additional dosing based on 28-day response per FDA label:

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

- Partial response is defined as organ improvement of at least one stage without worsening any other organ.
- Mixed response is defined as improvement of at least one evaluable organ with worsening in another organ per International Blood and marrow Transplantation Registry Severity Index criteria grading system

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

Approval of remestemcel was based on multiple trials including NCT02336230 (MSB-GVHD001) and NCT02652130 (MSB-GVHD002) as well as data from the expanded access program for aGvHD.

NCT02336230 is a phase 3, prospective study of the efficacy of remestemcel for the treatment of primary, steroid resistant acute GvHD grade B, C, or D compared to best available care. Best available care refers to the use of the best available therapeutic regimen not including the study therapy. The study population was comprised of 54 participants aged 2 months to 17 years of age without prior therapy for aGvHD other than steroids. The median age was 7 years old. Participants with grade B aGVHD with skin involvement only were excluded. Remestemcel was dosed based on weight and given via intravenous infusion twice per week for four consecutive weeks. The first outcome assessment occurred at day 28. Steroid therapy could be continued during the initial 28-day period, along with their established prophylactic GvHD regimen. Patients receiving other first or second line therapies were excluded (Kurtzberg 2020).

The primary endpoint was overall response (OR) at day 28 as compared to controls treated with best available care. The endpoint was met if the overall response in the remestemcel treatment group was greater than the OR in the best available treatment group. Not only did OR in the remestemcel group have to be better than the best available treatment group, but it also had to be better by 20% or more. Thirty-eight participants in the treatment group met this criterion. Those thirty-eight participants in the remestemcel group had an overall response of 70.4% as compared to best available care control group whose OR was 45%. Of the 38 people who met the OR primary endpoint, 29.6% had a complete response and partial responders were 40.9%. The median duration of response was 146 days (Kurtzberg 2020). Overall response rates were similar at day 28 and day 100 across age groups. There were 14 deaths in the first 100 days of therapy.

A follow-up, safety extension study (MSB-GVHD002, NCT02652130) enrolled 32 patients through 180 days. Most, (87.5%) were GvHD free without immunosuppression by day 180. There were two more deaths by day 180; none were

attributed to remestemcel therapy. Overall survival at day 180 in patients with grade C and grade D GvHD was 73.9% & 68% respectively. All patients had treatment-emergent adverse events but only 17% were thought to be attributable to Ryoncil; most were nonserious, and all recovered from the adverse event.

Another study reported in 2020 by Kurtzberg also indicated positive benefit of remestemcel used as salvage therapy in pediatric patients with aGvHD. NCT00759018 enrolled a total of 241 children with or without secondary immunosuppressive therapies for the treatment of steroid resistant GvHD grade B-D. Remestemcel was given as part of an expanded protocol that included eight biweekly infusions for a total of 28 days. An option of additional weeks of infusions were available if needed after the initial infusion. Overall response was observed in 157 patients (65%) by day 28. Safety was similar to the previously reported study MSB-GVHD001.

National and Specialty Organizations

There are no guidelines that have integrated the use of remestemcel for the management of acute graft verse host disease yet.

SUPPLEMENTAL INFORMATION

Grades refer to the overall severity of aGVHD. The overall grade is determined by the combination of organ stages.
International Bone marrow transplant registry severity index:

A- Stage 1: Skin involvement; no liver or gut involvement
B- Stage 2: Skin involvement; stage 1 or 2 gut or liver involvement
C- Stage 3: Skin, liver, or gut involvement
D- Stage 4: Skin, liver, or gut involvement

Table 1: Stage descriptions refer to the extent of each individual organ involvement

Organ	Stage	Description
Skin	1	Maculopapular rash over <25% of body area
	2	Maculopapular rash over 25 to 50% of body area
	3	Generalized erythroderma
	4	Generalized erythroderma with bullous formation and often with desquamation
Liver	1	Bilirubin 2.0 to 3.0 mg/dL
	2	Bilirubin 3.1 to 6.0 mg/dL
	3	Bilirubin 6.1 to 15.0 mg/dL
	4	Bilirubin >15.0 mg/dL
Gut	1	Diarrhea >30 mL/kg or >500 mL/day
	2	Diarrhea >60 mL/kg or >1000 mL/day

	3	Diarrhea >90 mL/kg or >1500 mL/day
	4	Diarrhea >90 mL/kg or >2000 mL/day; or severe abdominal pain with or without ileus

CODING & BILLING INFORMATION

CPT (Current Procedural Terminology)

Code	Description
96413	Chemotherapy administration, intravenous infusion technique; up to 1 hour, single or initial substance/drug
96415	Chemotherapy administration, intravenous infusion technique; each additional hour (List separately in addition to code for primary procedure)

HCPCS (Healthcare Common Procedure Coding System)

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

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

02/12/2025 New policy. IRO Peer Review on February 5, 2025 by a practicing physician board-certified in Pediatric Hematology/Oncology.

REFERENCES

1. 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. 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.
2. Elgaz S, Kuçi Z, Kuçi S, Bönig H, Bader P. Clinical Use of Mesenchymal Stromal Cells in the Treatment of Acute Graft-versus-Host Disease. Transfus Med Hemother. 2019 Feb;46(1):27-34. doi: 10.1159/000496809. Epub 2019 Feb 4. PMID: 31244579; PMCID: PMC6558336.
3. Kurtzberg J, Prockop S, Chaudhury S, Horn B, Nemecek E, Prasad V, Satwani P, Teira P, Hayes J, Burke E; MSB-275 Study Group. Study 275: Updated Expanded Access Program for Remestemcel-L in Steroid-Refractory Acute Graft-versus-Host Disease in Children. Biol Blood Marrow Transplant. 2020 May;26(5):855-864. doi: 10.1016/j.bbmt.2020.01.026. Epub 2020 Feb 7. PMID: 32044400; PMCID: PMC8292970.
4. ClinicalTrials.gov. National Library of Medicine. NCT02336230: 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) Accessed January 1, 2025. http://clinicaltrials.gov.
5. ClinicalTrials.gov. National Library of Medicine. NCT02652130. Safety Follow-up of Treatment With Remestemcel-L in Pediatric Participants Who Have Failed to Respond to Steroid Treatment for Acute GVHD. Accessed January 2, 2025. http://clinicaltrials.gov.
6. Remestemcel (Ryoncil) Package insert United States Food and Drug Administration (FDA). Approved December 2024. Package Insert – RYONCIL.
7. National Comprehensive Cancer Network V2.2024 Hematopoietic Cell Transplantation (HCT) guidelines
8. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. Br J Haematol. 1997 Jun;97(4):855-64. doi: 10.1046/j.1365-2141.1997.1112925.x. PMID: 9217189.