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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RYONCIL® safely and effectively. See full prescribing information for RYONCIL®.

RYONCIL® (remestemcel-L-rknd) suspension for intravenous infusion
Initial U.S. Approval: December 2024

INDICATIONS AND USAGE

RYONCIL is an allogeneic bone marrow-derived mesenchymal stromal cell (MSC) therapy indicated for the treatment of steroid-refractory acute graft versus host disease (SR-aGvHD) in pediatric patients 2 months of age and older.

DOSAGE AND ADMINISTRATION

For intravenous use only.

- The recommended dosage of RYONCIL is 2 × 10⁶ MSC/kg body weight per intravenous infusion given twice per week for 4 consecutive weeks. Infusions should be administered at least 3 days apart.
- Assess response 28 ± 2 days after the first dose and administer further treatment as appropriate as described in the table below.

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)

DOSAGE FORMS AND STRENGTHS

RYONCIL is available as a cell suspension for intravenous infusion in a target concentration of 6.68 X 10⁶ MSCs per mL in 3.8 mL contained in a 6 mL cryovial. (3)

CONTRAINDICATIONS

Known hypersensitivity to dimethyl sulfoxide (DMSO) or Porcine and Bovine proteins. (4)

WARNINGS AND PRECAUTIONS

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)

ADVERSE REACTIONS

The most common non-laboratory adverse reactions (incidence ≥20%) are: viral infectious disorders, bacterial infectious disorders, infection – pathogen unspecified, pyrexia, hemorrhage, edema, abdominal pain and hypertension (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Mesoblast at toll-free phone #1-844-889-MESO (6376) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

See 17 for PATIENT COUNSELING INFORMATION

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RYONCIL is indicated for the treatment of steroid refractory acute graft versus host disease (SR-aGvHD) in pediatric patients 2 months of age and older.

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

2.1 Recommended Dosage

- The recommended dosage of RYONCIL is 2×10^6 mesenchymal stromal cell (MSC)/kg body weight per intravenous infusion given twice a week for 4 consecutive weeks for a total of 8 infusions. Administer infusions at least 3 days apart.
- Assess response 28 ± 2 days after the first dose and administer further treatment as appropriate as described in Table 1 based on Day 28 response.

Table 1: Recommended Treatment based on Day 28 Response

Response	Recommendation
Complete Response	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 complete response	Repeat administration of RYONCIL twice a week for an additional 4 consecutive weeks (8 infusions total)

*Partial response defined as organ improvement of at least one stage without worsening in any other organ, whereas mixed response was defined as improvement of at least one evaluable organ with worsening in another organ as per International Blood and Marrow Transplantation Registry Severity Index Criteria grading system.

2.2 Preparation and Administration Instructions

Receipt and Storage of RYONCIL

RYONCIL is shipped directly to the clinical facility in a liquid nitrogen dry shipper maintained at a temperature of $\leq -135^\circ\text{C}$.

RYONCIL must remain frozen at $\leq -135^\circ\text{C}$ in liquid nitrogen vapor phase until thawed immediately prior to administration [see *How Supplied/Storage and Handling (16)*].

Preparation

RYONCIL and Plasma-Lyte® A should be prepared following aseptic technique in a Biological Safety Cabinet (BSC). Spray and wipe down the following materials with 70% alcohol prior to transferring them into the BSC preparation area. All materials should remain in the BSC preparation area unless discarded.

Prepare a sterile water bath to a minimum depth of 4 inches and warm to 37°C ($\pm 2^\circ\text{C}$) at least 30 minutes prior for thawing.

Supplies needed for preparation of RYONCIL and Plasma-Lyte® A

- RYONCIL vials
- Plasma-Lyte® A
- Infusion bag
- Interlink blood bag spikes (2)
- Interlink threaded lock cannula (1 per syringe)
- 60 mL luer-lock syringe (1)
- 5 mL luer-lock syringe (1 per each thawed vial)
- 18-gauge needle (1 per each thawed vial)
Note: Use a 1mL syringe if volume to be removed from vial is less than 1mL
- Airtight zip seal plastic bag(s) (1 per each vial for thaw)
- Water bath
- Alcohol wipes

Note: Plasma-Lyte® A may be substituted by Plasma-Lyte® 148 (pH 7.4 with no glucose).

Preparation of Plasma-Lyte® A

- 1- Insert the Interlink blood bag spike into the Plasma-Lyte® A bag.
- 2- Aseptically attach the threaded lock cannula to a 60 mL syringe.
- 3- Use an alcohol wipe to scrub the membrane of the Plasma-Lyte® A bag interlink spike injection site.
- 4- Attach the threaded lock cannula/syringe assembly to the Plasma-Lyte® A bag to the injection site.
- 5- Measure and withdraw 40 mL of Plasma-Lyte® A from the bag

Note: DO NOT remove the syringe containing Plasma-Lyte® A from the Plasma-Lyte® A bag. Set aside for later use.

Preparation of RYONCIL

1. Prior to RYONCIL thaw, verify that the pre-arranged time for the RYONCIL administration is still feasible. Patient infusion must occur within 5 hours from the start time of first vials of RYONCIL thaw.
2. Remove RYONCIL vial(s) from cryo-storage.
3. Place vial(s) into an airtight zip seal plastic bag(s) and immerse closed bag(s) into the water bath (37°C), maintaining the top closure above the water line. Use a separate zip seal plastic bag for each vial of RYONCIL.

Note: A maximum of 4 vials can be thawed in the water bath at the same time.

4. To thaw, gently agitate the sealed zip seal bag(s) with the vial(s) for approximately 5 to 8 minutes to thaw.
5. Remove vials from the water bath prior to the last visible crystal of ice melting.

Note: Do not exceed 15 minutes for each set of four vials.

6. Inspect vial(s) while still in the bag(s) to identify there is no leakage of vial contents.
7. Remove the RYONCIL vial(s) from the sealed plastic bag(s).

8. Inspect for foreign particulate matter (FPM). If FPM is found via visual inspection – DO NOT USE! Retain the offending vial(s). Call the Mesoblast contact number 844-889-MESO (6376).
9. Wipe RYONCIL vial(s) and top cap(s) with 70% alcohol. Wipe off any excess liquid.
10. Promptly withdraw the required amount of RYONCIL (based on actual patient body weight) from the vial(s). One syringe and an 18-gauge needle per thawed vial is required.
11. Carefully remove the needle from the syringe containing RYONCIL.
12. Attach the threaded lock cannula to the syringe.
13. Retrieve the infusion bag.
14. Wipe the membrane of the infusion bag interlink spike injection site with sterile alcohol wipe.
15. Insert 1 interlink blood bag spike into the outermost port on the infusion bag (leave the middle port for the infusion line.)
16. Attach the syringe to the spike and transfer the RYONCIL into the infusion bag.
17. Remove the syringe with the threaded lock cannula and discard the syringe and the threaded lock cannula.
18. Repeat for each syringe until the required volume of RYONCIL is added to the infusion bag.

Transfer of Plasma-Lyte® A into Infusion Bag

1. Retrieve the bag and 60 mL syringe containing Plasma-Lyte® A.
2. Verify the syringe contains 40mL of Plasma-Lyte® A.
3. Aseptically remove the 60 mL syringe with the threaded lock cannula containing the 40mL Plasma-Lyte® from the bag of Plasma-Lyte® A.
4. Use alcohol wipes to clean the membrane of the infusion bag interlink spike injection site.
5. Aseptically attach the 60mL syringe containing the Plasma-Lyte® A to the spike.
6. Slowly transfer the 40mL Plasma-Lyte® A into the infusion bag.
7. Gently mix cells with the Plasma-Lyte® A.
8. Remove the syringe with the threaded lock cannula and discard the syringe and threaded lock cannula.
9. Label the bag according to Institutional Policy.
10. Transport infusion bag to patient infusion area.

Administration

Note: Patient infusion must occur within 5 hours from the start time of first vial(s) of RYONCIL thaw.

- Administer RYONCIL under the supervision of a qualified health professional experienced in the management of SR-aGvHD.
- Administer RYONCIL using an infusion pump.
- Use blood filter with a pore size of 40-260 microns for infusion of RYONCIL.

- Flush lines per institutional practice and/or policy for cellular infusions.
- Pretreatment
Premedicate patients with corticosteroids and antihistamines 30-60 minutes prior to administration of RYONCIL to reduce the potential for infusion reactions.
- Infusion Rates
 - For patients weighing 35 kg or more, infuse RYONCIL at a rate of no more than 6mL/ minute.
 - For patients weighing less than 35 kg, infuse RYONCIL over the course of 60 minutes.
- Discard unused, thawed RYONCIL vials per institutional policy.

3 DOSAGE FORMS AND STRENGTHS

RYONCIL is available as a cell suspension for intravenous infusion in a target concentration of 6.68 X 10⁶ MSCs per mL in 3.8 mL at cryopreservation contained in a 6 mL cryovial.

Each 6 mL cryovial contains approximately 25 x 10⁶ MSCs.

Cryopreserved MSCs are combined with Plasma-Lyte[®] A for administration.

4 CONTRAINDICATIONS

Do not use RYONCIL in patients with known hypersensitivity to dimethyl sulfoxide (DMSO) or porcine and bovine proteins.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity and Acute Infusion Reactions

Hypersensitivity reactions including acute infusion reactions have occurred with RYONCIL administration [see *Adverse Reactions (6.1)*]. Serious hypersensitivity reactions, including anaphylaxis, may occur due to DMSO and trace amounts of porcine or bovine proteins. Signs and symptoms may include fever, dyspnea, and hypotension during or after RYONCIL infusion.

Premedicate patients with antihistamine and corticosteroids and monitor closely for signs and symptoms of hypersensitivity or acute infusion reactions.

If a hypersensitivity or infusion reaction occurs, interrupt RYONCIL infusion. Do not administer RYONCIL in patients who experience serious or life-threatening reactions.

5.2 Transmission of Infectious Agents

Transmission of infectious disease or agents may occur with RYONCIL administration because it contains cells from human donors and is manufactured using human, porcine and bovine-derived reagents. Donors are screened and tested for Human Immune-deficiency Virus 1 (HIV-1); Human Immune-deficiency Virus 2 (HIV-2); Hepatitis B Virus (HBV); Hepatitis C Virus (HCV); Human T-cell Leukemia-lymphoma Virus 1 (HTLV-1); Human T-cell Leukemia-lymphoma Virus 2 (HTLV-2); West Nile Virus (WNV); Cytomegalovirus (CMV); Epstein-Barr Virus (EBV); and Syphilis (*Treponema pallidum*). Only screening was performed for Creutzfeldt-Jakob disease (CJD) and communicable disease risks associated with xenotransplantation. RYONCIL cell banks are tested for human and animal viruses, retroviruses, bacteria, fungi, yeast, and mycoplasma. Human and animal-derived

reagents are tested for human and animal viruses, bacteria, fungi, and mycoplasma before use. These measures do not eliminate the risk of transmitting these or other infectious diseases or agents.

5.3 Ectopic Tissue Formation

Ectopic tissue formation may occur following treatment with RYONCIL due to the ability of human mesenchymal stromal cells to differentiate into mesenchymal lineage cells such as bone, cartilage and fat cells.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

The safety data described in this section reflect exposure to RYONCIL in 54 patients in Study MSB-GVHD001 for the treatment of SR-aGvHD. Patients received intravenous infusion of RYONCIL 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 weeks [see *Clinical Studies (14)*]. The median number of doses administered were 10 (range 1 to 16), and the treatment was administered over a median of 43 days (range 1 to 104 days).

Serious adverse reactions occurred in 35 patients (65%) including pyrexia (n=5;9%), respiratory failure (n=5;9%), pneumatosis intestinalis (n=4;7%) and staphylococcal bacteremia (n=2;<5%). Eight patients had discontinuation of RYONCIL treatment due to the following: acute infusion reactions (n=3), hypotension (n=1), gastroenteritis (n=1), and death (n=3).

Table 2 summarizes most common adverse reactions that occurred in $\geq 10\%$ patients in Study MSB-GVHD001.

Table 2: Adverse Reactions Occurring in $\geq 10\%$ of Patients in Study MSB-GVHD001 (N=54)**

Adverse Reactions	All Grades ^a n (%)	Grade 3 ^b n (%)
Viral infectious disorders*	30 (56)	8 (15)
Bacterial infectious disorders*	24 (44)	10 (19)
Infections - pathogen unspecified*	22 (41)	8 (15)
Pyrexia	19 (35)	2 (4)
Hemorrhage*	15 (28)	4 (7)
Edema*	12 (22)	1 (2)
Abdominal pain	11 (20)	4 (7)
Hypertension	11 (20)	3 (6)
Vomiting	10 (19)	3 (6)
Arrhythmia*	9 (17)	2 (4)
Diarrhea	9 (17)	1 (2)
Rash*	9 (17)	0 (0)
Arthralgia	8 (15)	0 (0)
Fungal infectious disorders*	8 (15)	2 (4)
Hypotension	8 (15)	2 (4)
Cough	7 (13)	0 (0)
Respiratory Failure	6 (11)	6 (11)

^a Based on National Cancer Institute Adverse Event Common Toxicity Criteria version 4.03

^b No grade 4 or 5 adverse reactions occurred in the study

*Is a composite that includes multiple related terms

**Includes adverse reactions up to 100 days following RYONCIL treatment

Table 3 presents the most common grade 3 or 4 laboratory abnormalities that worsened from baseline in ≥10% of patients

Table 3: Grade 3 or 4 Laboratory Abnormalities that Worsened from Baseline in ≥ 10% of Patients in Study MSB-GVHD001 (N=54)

Laboratory Parameter	Grade 3 or higher ^a %
Gamma-glutamyl transferase increased	32
Thrombocytopenia	28
Blood bilirubin increased	11
^a Based on National Cancer Institute Adverse Event Common Toxicity Criteria version 4.03	

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data for RYONCIL use in pregnant women. No animal reproductive and developmental toxicity studies have been conducted with RYONCIL to assess whether it can cause fetal harm when administered to a pregnant woman. It is not known if RYONCIL has the potential to be transferred to the fetus. Therefore, RYONCIL is not recommended for women who are pregnant. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 10-20%, respectively.

8.2 Lactation

Risk Summary

There is no information regarding the presence of RYONCIL in human milk, the effect on the breastfed infant, and the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RYONCIL and any potential adverse effects on the breastfed infant from RYONCIL or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of RYONCIL for treatment of SR-GvHD have been established in pediatric patients 2 months of age and older. The use of RYONCIL in these age groups is supported by evidence from an adequate and well-controlled trial [see *Adverse Reactions (6) and Clinical Studies (14)*].

11 DESCRIPTION

RYONCIL is provided as a frozen cell suspension in a cryogenic vial. The active ingredient in RYONCIL is comprised of culture-expanded mesenchymal stromal cells (MSCs) isolated from the bone marrow of healthy human adult donors. Each cryovial contains nominally 25 x 10⁶ MSCs in 3.8 mL (a target

concentration 6.68×10^6 cells/mL) formulated in Plasma Lyte[®]-A (70% v/v), Human Serum Albumin (HSA) Solution (25%) (20% v/v) and Dimethyl sulfoxide (DMSO) (10% v/v). The product is thawed and combined with Plasma-Lyte[®] A prior to intravenous administration.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action for RYONCIL is not clear but may be related to immunomodulatory effects. Data from in vitro studies demonstrate that MSCs inhibit T cell activation as measured by proliferation and secretion of pro-inflammatory cytokines. Acute GvHD occurs when alloreactive donor-derived T cells within the donated tissue (graft) trigger an immunological response, and alloreactive donor-derived T cells play a role in mediating the systemic inflammation, cytotoxicity and potential end organ damage associated with aGvHD.

12.2 Pharmacodynamics

Human pharmacodynamic data were obtained from analysis of blood samples in pediatric subjects with SR-aGvHD (n=40; age range 0.6-17 years) following treatment with RYONCIL at a dose of 2×10^6 cells/kg. At Baseline, elevated levels of tumor necrosis factor receptor type I (TNFR1) and suppressor of tumorigenicity 2 (ST2) were observed consistent with the inflammatory state of aGvHD. Treatment with RYONCIL reduced the levels of TNFR1 and ST2 by 79% and 75%, respectively, at Day 180 as compared to baseline values. Further, the circulating levels of CD3+CD4+CD25+HLA-DR+ T cells, which represent activated T cells, were reduced by 64% at Day 180 following treatment with RYONCIL as compared to the baseline values.

12.3 Pharmacokinetics

No studies have been performed to evaluate the pharmacokinetics of RYONCIL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been performed to evaluate the effects of RYONCIL on carcinogenesis, mutagenesis or impairment of fertility.

14 CLINICAL STUDIES

The efficacy of RYONCIL was evaluated in a multicenter, prospective, single-arm study (MSB-GVHD 001; NCT02336230). 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 (IBMTR) after receiving allogeneic hematopoietic stem cell transplantation (HSCT). 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 HSCT. 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.

The efficacy results are summarized in Table 4.

Table 4: Efficacy Results for Study MSB-GVHD001

Response at Day 28	N=54
Overall Response Rate n (%) 95% CI ^a	38 (70%) 56.4, 82.0
Duration (days) Median (range)	54 (7, 159+)
Complete Response Rate n (%) 95% CI ^a	16 (30%) 18.0, 43.6
Partial Response Rate ^d n (%) 95% CI ^a	22 (41%) 27.6, 55.0

CI=confidence interval

^a Two-sided exact binomial confidence interval at the 95% level

^b Duration of response was calculated from Day-28 response to either progression (worsening by one stage in any organ without improvement in other organs in comparison to prior response assessment), new systemic therapy for aGvHD or death from any cause.

^c Complete response was defined as resolution of aGvHD in all involved organs as per IBMTR grading system.

^d Partial response was defined as organ improvement of at least one stage without worsening of any other organ as per IBMTR grading system.

Overall response rate at Day 28 by baseline disease severity is as follows: Grade B (3/6; 50%), Grade C (16/23; 70%), and Grade D (19/25; 76%).

Among the 38 responders, the median time from Day-28 response to either death or need for systemic therapy for aGvHD (non-RYONCIL systemic therapy for aGvHD or increase in the dose of corticosteroids to methylprednisolone 2 mg/kg or equivalent) was 111.5 days (range 9, 182+).

16 HOW SUPPLIED/STORAGE AND HANDLING

RYONCIL is supplied as a sterile, cryopreserved cell suspension of ex-vivo culture-expanded allogeneic bone marrow-derived mesenchymal stromal cells (MSC) in vials in the following package sizes:

NDC Number	Presentation	Package Size
73648-154-01	Single-Use Vial (target 25×10^6 MSCs in 3.8 mL)	Carton containing 1 vial
73648-154-04	Single-Use Vial (target 25×10^6 MSCs in 3.8 mL)	Carton containing 4 vials

RYONCIL is shipped to the clinical facility in a liquid nitrogen dry shipper maintained at a temperature of $\leq -135^\circ\text{C}$.

Storage conditions: RYONCIL must remain frozen at $\leq -135^\circ\text{C}$ in liquid nitrogen vapor phase until thawed immediately prior to administration.

Handling: Restrict preparation and administration of RYONCIL to a medical facility in which the medical personnel are trained in aseptic technique.

Disposal: Dispose empty or partially used RYONCIL vials according to the institutional guidelines for disposal of biohazard materials.

Do not save reconstituted RYONCIL vials for future use.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients and/or caregivers.

- Hypersensitivity and Acute infusion reactions: Inform patients and/or caregivers that hypersensitivity and acute infusion reactions due to the presence of porcine and bovine protein, and DMSO may occur with RYONCIL infusion. Advise patients and/or caregivers to seek immediate medical evaluation if any signs and symptoms of hypersensitivity or acute infusion reactions occur, such as fever, rash or hives, low blood pressure, breathing problems [see *Warnings and Precautions (5.1)*].
- Transmission of Infectious Agents: Inform patients and/or caregivers about the possible risk of transmission of infectious agents with RYONCIL administration [see *Warnings and Precautions (5.2)*].
- Ectopic Tissue Formation: Inform patients and/or caregivers about the possible risk of ectopic tissue formation with RYONCIL administration [see *Warnings and Precautions (5.3)*].

Manufactured for:

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