



Memorandum

DATE: July 10, 2020

TO: Upendra Mahat, MD,
CBER/OTP/OCE/DCEH/MHB

Matthew Klinker, Ph.D.
CBER/OTP/OCTHT/DCT1/CTB2

FROM: Michael Brony, Pharm.D.
CBER/OCBQ/DCM/APLB

THROUGH: Lisa L. Stockbridge, Ph.D.
CBER/OCBQ/DCM/APLB

SUBJECT: Labeling Review
RYNCIL™ (remestemcel-L-rknd)
BLA 125706/0.
Sponsor: Mesoblast Inc.

Background: The sponsor submitted:

New Approval
 Changes Being Effected (CBE) supplement
 Prior Approval Supplement (PAS) Amendment
 Major Amendment

Submission contains:

Prescribing Information (PI)
 Patient Package Insert (PPI)
 Package and/or container labels
 Other (Medication Guide)

Resubmission Date: January 31, 2023

Action Due Date: August 2, 2023

APLB Comments/Recommendations

Mesoblast Inc. resubmitted a Biologics License Application (BLA) for RYONCIL (remestemcel-L-rknd), *ex-vivo* culture-expanded adult human mesenchymal stromal cells (ce-MS-C)) suspension for intravenous infusion, for the treatment of acute Graft versus Host Disease (aGvHD) in pediatric patients, when the aGvHD has been refractory to treatment with systemic corticosteroid therapy (SR-aGVHD).

APLB has reviewed the draft PI and labels from a promotional and comprehension perspective and offer the following comments:

GENERAL COMMENTS

- Use command language wherever possible (e.g. DOSAGE AND ADMINISTRATION).
 - Unless study is closed, refrain from using National Clinical Trial (NCT) numbers. Use of the number in the PI provides tacit approval for everything in the trial and may be used in promotion.
 - Do not refer to study numbers in the PI. This is uninformative. Instead, describe the study where applicable.
 - Do not capitalize common nouns. Overuse of capitalization diminishes readability.
 - Do not use international spelling.
 - Avoid vague terms with no established definitions or quantification.
 - Mild, moderate, severe
 - Well-tolerated
 - Rare
 - Use caution
 - Avoid research terminology (e.g., Phase 1, 2, 3, pivotal), as not all end users are academic researchers. Simply describe the clinically significant data regarding safety and effectiveness.
 - Use bullets to increase readability.
 - Only use bolding on headings and statements as required by the regulations. Overuse of bolding minimizes its importance.
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HIGHLIGHTS

- The first line of the product title should include the proprietary name and proper name. Do not include the description. Place the dosage form and route of administration of biological products outside of the parentheses. If space is limited, these may be presented on a second line. Thus, the product title for RYONCIL should look like this:

RYONCIL (remestemcel-L-rknd) suspension for intravenous use

- Revise the indication to follow the regulatory format:

[TRADENAME] is a [product class name] that is indicated for [indication(s)].

- Revise the DOSAGE AND ADMINISTRATION section to active voice. Consider bullets or a table to improve readability. It is not necessary to use the term “recommended” when describing dose. Implicitly, the PI provides the instructions for safe and effective use, including the recommended dose.
- Is there a limit to the number of times that treatment can be repeated? If so, this should be included in DOSAGE AND ADMINISTRATION.
- Ensure that the WARNINGS AND PRECAUTIONS reflect section 5 WARNINGS AND PRECAUTIONS of the FULL PRESCRIBING INFORMATION.
- The sentence under ADVERSE REACTIONS is not informative. For this section, use a statement of the most common adverse reactions with a cut-off frequency. Do not include serious adverse reactions in the list of common adverse reactions (there may be another sentence for serious adverse reactions, if necessary). Refrain from using the promotional term, “infrequent,” as this minimizes the risks that do occur. For example:

The most common adverse reactions (n ≥ 5%) in the clinical studies were hemolytic uremic syndrome, neutropenia; thrombocytopenia; nausea; vomiting; pyrexia; graft-versus-host disease in skin, adenovirus infection; cytomegalovirus infection; BK virus infection; hypermetabolism; somnolence, and hypotension.
- Add a space between ADVERSE REACTIONS and the directive regarding the presence of section 17 PATIENT COUNSELING INFORMATION and the Medication Guide.
- Since this is a new application, please remove *Revised: [date]*.

FULL PRESCRIBING INFORMATION: CONTENTS

- Ensure that headings match the FULL PRESCRIBING INFORMATION (FPI).
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FULL PRESCRIBING INFORMATION (FPI)

1 INDICATIONS AND USAGE

This section should have at least as much information as the corresponding section in the HIGHLIGHTS. The regulatory statement from the HIGHLIGHTS may be used here as well.

2 DOSAGE AND ADMINISTRATION

- Immediately following the heading, DOSAGE AND ADMINISTRATION, please include the bolded, sentence case statement “**For intravenous use only.**” and delete this statement from subsection 2.1.
- For consistency with similar biologic product labeling, please organize this section into two or three subsections:
 - **2.1 Dose**
 - **2.2 Administration**or
 - **2.1 Dose**
 - **2.2 Preparation**
 - **2.3 Administration**
- For readability and comprehension, revise this section to active voice. Provide clear and concise directions. Eliminate statements that are purely practice of medicine or attempts to limit the use of this product, which is not being provided under limited distribution.
- Pretreatment should be at the top of the administration subsection, not after all the information regarding administration.
- Consider a table or chart for the different administration conditions by weight. Provide the same units for timing the infusion rate.
- Consider adding figures to the steps of preparation for administration.
- The following sentence appears promotional:

(b) (4)

If it is not true, please delete. If it is true, please revise.

- Please include the following required statement:

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

- Include the expected color of the suspension.

5 WARNINGS AND PRECAUTIONS

- Revise the wording in this section to active voice.
- Simply describe data without using study numbers. These are not informative to the safe and effective use of the product.
- In subsection 5.1 Hypersensitivity Reactions, consider adding detail regarding the signs and symptoms that should be considered when monitoring for hypersensitivity reactions to this product. For example, section 17 PATIENT COUNSELING INFORMATION states that somnolence is one of the signs and symptoms of a hypersensitivity reaction to porcine or bovine proteins in RYONCIL.
- The theoretical risks of ectopic tissue formation and malignancy may be combined. Consider language similar to the theoretical risk of transmission of infectious agents. The current statement, that there were no cases in clinical studies, minimizes the risk that this can occur at all.

6 ADVERSE REACTIONS

- Directly beneath the section heading restate the most common adverse reactions, along with a cut-off frequency, that is found in the HIGHLIGHTS.
- The statement, *Adverse reactions were infrequent and are discussed in detail in section 6.1*, is promotional and should be deleted.
- Only adverse reactions, as defined in 21 CFR §201.57(c)(7), should be included in this section. The regulatory definition of an adverse reaction is an undesirable effect, reasonably associated with the use of a product, which may occur as part of the pharmacological action of the product or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a product, only those for which there is some basis to believe there is a causal relationship between the product and the occurrence of the adverse event. Serious adverse reactions are further defined as adverse reactions that cause death or discontinuation.

The above excerpt is unnecessary given the table that follows, and the last sentence, if accurate, should read: "There were no serious adverse reactions reported in RYONCIL this study."

8 USE IN SPECIFIC POPULATIONS

Revise the language used in subsection 8.4. This subsection must summarize the data presented elsewhere and cross reference to that information. Remove the informal language, “discussed throughout this labeling document.”

12 CLINICAL PHARMACOLOGY

- Subsection 12.2 Pharmacodynamics should be a description of biochemical or physiologic clinical effects, adverse reactions, or toxicity. However, the first paragraph of the proposed subsection 12.2 Pharmacodynamics is describing allograft survival based on an animal model. This type of information does not belong in 12 CLINICAL PHARMACOLOGY. Consideration for its inclusion in 13 NONCLINICAL PHARMACOLOGY may be warranted (see below).

Ensure that this subsection includes data on exposure-response relationship and time course in humans. If this is not known, include a statement about lack of information.

14 CLINICAL STUDIES

- Do not bold headings for sub-subsections. Use italics and/or underlining if a sub-subsection heading is necessary.
- Do not have subsections in 14 unless you have more than one indication.
- For readability, consider presenting each study as paragraphs under the one header rather than subsectioning.

PACKAGE/CONTAINER LABELS

We have no comments at this time.

If you have any questions regarding this review please contact Michael Brony, Pharm.D. at 240-402-8898.
