



Memorandum

Date: August 26, 2021

To: Adriane Fisher, MPH, MBA, CBER/OTAT/DRPM/RPMBI
Thomas Finn, PhD, CBER/OTAT/DCGT/CTB

From: Michael Brony, Pharm.D.
Regulatory Review Officer
Advertising and Promotional Labeling Branch (APLB)
Division of Case Management

Through: Lisa L. Stockbridge, Ph.D.
Branch Chief
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Division of Case Management

Subject: Labeling Review
RETHYMIC (Allogeneic Processed Thymus Tissue)
STN # 125685/0
Sponsor: Enzyvant Therapeutics GmbH

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)

Submission Date: April 9, 2021

PDUFA Action Date: October 8, 2021

APLB Comments/Recommendations

On April 9, 2021, Enzyvant Therapeutics GmbH submitted a Class 2 Resubmission-Response to a December 4, 2019, Complete Response Letter (CRL) for RETHYMIC (STN 125685/0). In their response, Enzyvant addressed manufacturing and analytical methodology issues outlined in the CRL. Enzyvant also provided additional clinical data and is now seeking full approval for the indication of immune reconstitution in pediatric patients with congenital athymia.

The following comments and recommendations are made from a promotional and comprehension perspective.

GENERAL

- Use command language (active voice), particularly in the DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS sections.
- Remove statements that clearly are practice of medicine. For example, *Surgical implantation of allogeneic processed thymus tissue product (RETHYMIC) should be done by a qualified surgeon.*
- Do not bold unless required by regulations or guidance.
- Do not number sub-subsection headings (e.g., 12.3.1 Metabolism). Instead, use italics or underlining to separate out sub-subsections of a subsection.

HIGHLIGHTS

- The indication should be stated in the following manner:

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

- Since this is an original application, please remove “Revised: March/2021”

TABLE OF CONTENTS (TOC)

Please ensure that the TOC is consistent with the FPL. There is no BOXED WARNING in the FPL.

FULL PRESCRIBING INFORMATION (FPL)

2 DOSAGE AND ADMINISTRATION

- Emphasize route of administration with a bolded, sentence case phrase placed directly beneath the section heading.
- Increase readability of step-by-step instructions with the use of active voice.

- For consistency with most labels, this section is usually organized in two or three subsections:

2.1 Dose
2.2 Administration

Or

2.1 Dose
2.2 Preparation
2.3 Administration

Please choose either one of these formats.

- Postoperative surgical management does not belong in this section. However, infection control and immunoprophylaxis may be important to the administration and follow-up of this transplant. Because of the dependence of postoperative treatment to the success of the administration of this product, such information is better suited for location here than as a first warning.
- There are no numbered sub-subsections in permitted in the content of labeling (Structured Product Labeling or SPL).

3 DOSAGE FORMS AND STRENGTHS

Administration information does not belong in this section.

5 WARNINGS AND PRECAUTIONS

- Ensure that the warnings and precautions are listed in decreasing order of severity and significance.
- Infection control and immunoprophylaxis would be a precaution related to administration rather than a first warning in WARNINGS AND PRECAUTIONS. Most of the information currently in this subsection belongs in the Administration subsection of DOSAGE AND ADMINISTRATION.
- Do not number sub-subsections. Instead use italics or underlining to present subheading in a subsection.

6 ADVERSE REACTIONS

- The information appearing between the section heading and subsection 6.1 should reflect the statement of the most common adverse reactions that appears in the HIGHLIGHTS. It reappears here to cover abbreviated stylesheets that do not subsection this section. It is not helpful to hyperlink "significant adverse

reactions” in WARNINGS AND PRECAUTIONS. The list presented is longer than the paragraph of most common adverse reactions and decreases the readability of the information presented.

- Subsection 6.2 is not required and may be deleted if there is no information.

8 USE IN SPECIFIC POPULATIONS

- Subsection 8.4 should contain a hyperlink to section 14 CLINICAL STUDIES.
- Subsection 8.5 is not relevant to this product and its indication. Subsection 8.5 may be deleted.
- Subsections 8.6 and 8.7 are not required and should be deleted if there are no data.

12 CLINICAL PHARMACOLOGY

- Delete the sentence, *No clinical pharmacology studies have been conducted with RETHYMIC*, appearing directly beneath this section heading. There are required subsections to this section even if there are no data.
- Subsections 12.2 Pharmacodynamics and 12.3 Pharmacokinetics are required and, if studies have not been conducted, they must state that there is a lack of information.

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