



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)**

PHARMACOVIGILANCE PLAN REVIEW FOR ORIGINAL BLA

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Subject: Review of Pharmacovigilance Plan

Applicant: Enzyvant Therapeutics GmbH

Product: Rethymic (Allogeneic Processed Thymus Tissue)

Application Number: BLA/ STN 125685/0

Proposed Indication: Rethymic™ is indicated for immune reconstitution in pediatric patients with congenital athymia

Submission Date: August 6, 2021

Action Due Date: Oct 8, 2021

1 OBJECTIVE

This review assesses the adequacy of the pharmacovigilance plan based on the safety profile of Rethymic (Allogeneic Processed Thymus Tissue).

2 PRODUCT INFORMATION

Background

T cell immunodeficiency due to congenital athymia is a rare life-threatening disorder that results in a patient's inability to develop naïve T cells and subsequently mount an appropriate immune response to infection. For the clinical diagnosis of athymia, the patient must have fewer than 50 naïve T cells/mm³ (CD45RA+CD62L+) in the peripheral blood on flow cytometry or have less than 5% of total T cells being naïve in phenotype. Without immune reconstitution, infants diagnosed with congenital athymia die from infection within the first few years of life.

T cell immunodeficiency due to athymia is associated with congenital disorders which prevent the development of a functional thymus, such as complete DiGeorge Anomaly (cDGA) and forkhead box protein N1 (FOXP1) deficiency. DiGeorge Syndrome is a clinically defined syndrome with the diagnosis based on the presence of cardiac anomalies, hypocalcemia, and reduced numbers of circulating T cells. Patients with reduced numbers of circulating T cells have what is called partial DGS. They have a small but functional thymus that produces naïve T cells. Partial DGS patients are capable of mounting an immune response to infections and do not typically die secondary to immunodeficiency. Their phenotype is different than the small group of DGS patients with athymia (absence of thymus) who have virtually no naïve T cells (T cell immunodeficiency); these athymic patients have what is called cDGA. cDGA occurs in less than 1% of patients with DGS; using a conservative 1% estimate, the estimated birth prevalence of cDGA would be approximately 0.02 to 0.05 in 10,000 births. FOXP1 deficiency is an exceptionally rare inherited disease with only 10 cases reported in the literature.

There are currently no treatments for congenital athymia except for cultured thymus tissue.

Product description

Allogeneic cultured postnatal thymus tissue product is a one-time regenerative therapy manufactured from tissue obtained from unrelated donors under the age of 9 months undergoing cardiac surgery. It is administered by a surgical procedure for immune reconstitution in pediatric patients with congenital athymia. It is often, though not always, co-administered with immunosuppressive therapy that is tailored to each patient. Regimens included RATGAM (rabbit derived anti-thymocyte gammaglobulin), RATGAM with cyclosporine, or RATGAM with tacrolimus. Steroids or mycophenolate could also be used.

Proposed dosing regimen(s) and formulation(s)

Rethymic tissue consists of yellow to brown slices of processed tissue, with a Rethymic slice defined as the contents on a single filter membrane. Each polystyrene culture dish contains up to 4 Rethymic slices that adhere to circular filter membranes on top of surgical sponges in 5 mL of media. As the Rethymic slices vary in size and shape, the dosage is based on the total surface area of the Rethymic slices. The amount administered is calculated based on recipient BSA. The surgeon should implant as many Rethymic slices as possible within the recommended dose range of (b) (4) to 22,000 mm² of Rethymic/m² recipient BSA.

The manufacturer calculates the dose in advance for the specific patient; the amount of product provided is adjusted at the manufacturing facility to ensure the maximum dose for the patient cannot be exceeded. The portion of the product that represents the minimum dose is communicated to the surgical team at the time of surgery. Up to 42 Rethymic slices are provided for each patient.

3 PERTINENT REGULATORY HISTORY

- Rethymic is currently not marketed in any country.
- Rethymic was granted orphan product designation on August 15, 2003.
- Enzyvant Therapeutics GmbH (Enzyvant) submitted the final package of rolling Biologics License Application (BLA) on April 5, 2019.
- Amendments were submitted and received on November 15, 2019 and November 26, 2019.
- The FDA sent a complete response letter on December 4, 2019. FDA could not grant final approval because of deficiencies in chemistry manufacturing and controls. Notable issues included lack of standardization in production of lots, sampling and testing for quality, and sterilization maintenance.
- After a Type A Meeting was conducted on March 19, 2020 and multiple extension requests, Enzyvant resubmitted their BLA on April 09, 2021.

4 MATERIALS REVIEWED

Materials reviewed in support of this assessment include:

- Applicant's Safety Management Plan: Safety Specification and Pharmacovigilance Plan for RETHYMIC™ (Allogeneic Processed Thymus Tissue-agdc), Version 3.0 (Module 1.11.4, 125685/0068)
- SOP-051 Post-Marketing Adverse Event and Product Complaint Handling and Reporting for Enzyvant Products, Version 3.0 (Module 1.11.4, 125685/0063)
- Annotated Prescribing Information (Module 1.11.3, 125685/0060)
- Introduction (Module 2.2, 125685/0060)
- Nonclinical Overview (Module 2.4, 125685/0003)
- Clinical Overview (Module 2.5, 125685/0003)
- Summary of Clinical Safety, resubmission (Module 2.7.4, 125685/0060)

- Study Reports of Uncontrolled Clinical Studies: Narratives of Deaths, Other Serious Events, and Other Specified Adverse Events (Module 5.3.5.2, 125685/0003)

5 CLINICAL SAFETY DATABASE

The clinical program for Rethymic consisted of 10 pediatric trials: 7 core clinical studies with patients with congenital athymia, 2 additional Investigational New Drug (IND) application protocols, and 1 non-IND study. All studies were open label with no control groups. Of note, there was considerable variability in patient diagnoses and phenotypic expression, resulting in substantial differences in treatment plans with or without immunosuppressive therapies. The table below describes the groups and studies in further detail.

Table 1: Rethymic clinical program

Study	No. of subjects	Objectives	Population and Treatment
668-1	14	Assessed the safety of thymus transplantation	Subjects with typical cDGA and who received no immunosuppression. Subjects with elevated T cell function received immunosuppression under individualized treatment plans.
668-2	12	Assess safety and efficacy as determined by survival; to assess thymopoiesis in the thymus graft and reconstitution of T cell function by flow cytometry and PCR	
884	12	Assessed safety, tolerability, and efficacy of thymus transplant with immunosuppression	Subjects with typical cDGA (but with elevated T cell function) and atypical cDGA received immunosuppression with RATGAM and cyclosporine.
931	5	Assessed thymus tissue and parental parathyroid transplantation	Subjects with typical and atypical cDGA and with hypoparathyroidism requiring calcium supplementation received 1 of 2 immunosuppression regimens: RATGAM only (Group 1) or RATGAM with either cyclosporine or tacrolimus (Group 2). Four out of 5 also received single parental parathyroid transplants.
932	7	Evaluated correlations between dose of thymus tissue transplanted and immunological outcomes after transplant	Subjects with typical cDGA received no immunosuppression.

950	15	Evaluated the safety and toxicity of thymus transplantation with immunosuppression tailored to subject immune status	Subjects with typical cDGA and lower PHA response received RATGAM only, while those with higher received RATGAM with either cyclosporine or tacrolimus. Subjects with atypical cDGA received RATGAM, steroids, and either cyclosporine or tacrolimus.
25966	28	Evaluated survival and the effect on immune function of thymus transplantation with immunosuppression regimens tailored to the subject's immune status	Subjects with typical and low PHA response received no immunosuppression or RATGAM only. RATGAM with either cyclosporine or tacrolimus was given to patients with typical cDGA and high PHA response or atypical cDGA. Patients with atypical cDGA and very high PHA responses or maternal engraftment received RATGAM with mycophenolate and either cyclosporine or tacrolimus.
(b) (6)	1	Single subject treatment plan: Thymus Transplantation for EBV Lymphoma	A subject with cDGA who had previously received infusions of peripheral blood mononuclear cells from a HLA-identical sibling received pre-transplantation immunosuppressive regimen of fludarabine and dexamethasone.
51692	10	Expanded access use in other conditions (hematologic malignancy, immunodeficiency, severe autoimmune disease related to poor thymic function, prior HCT)	Subjects with poor thymic function from immunodeficiency, hematologic malignancies, or severe autoimmune disease received tailored immunosuppressive therapies that varied greatly between patients. Adjunctive therapies (including bone marrow transplantation with myeloablation, chemotherapy for malignancy, and cytotoxic lymphocyte infusions for viral infections) were allowed.
735	1	Treatment of subjects with partial DGS	A subject with partial DGS with prolonged significant T cell dysfunction and infections were treated with RVT-802 implantation

			without immunosuppressive therapy.
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The race of the subjects in the clinical program was: 72.4% White, 20.0% Black or African American, 2.9% Asian, 1.9% American Indian or Alaska Native, 1.0% Native Hawaiian or other Pacific Islander, and 1.9% more than one race. The median age at implantation was 269 days old (range 33-6163 days old).

Summary of Adverse Events

All 105 subjects in the clinical program experienced at least one adverse event (AE) within the first two years of implantation. The most common AEs reported in >20% of subjects were: pyrexia (62/59.0%), device-related infection (51/48.6%), rash (33/31.4%), hypertension (30/28.6%), diarrhea (29/27.6%), hypoxia (27/25.7%), alanine aminotransferase (ALT) increased (26/24.8%), thrombocytopenia (24/22.9%), anemia (23/21.9%), and aspartate aminotransferase (AST) increased (23 (21.9%).

There were 515 serious AEs (SAEs) in 89 (84.8%) subjects. The most frequently reported preferred terms (PTs) and their corresponding system organ class (SOC) are shown in Table 2.

Table 2: SOC with SAEs reported in >5% of Subjects

SOC Preferred Term	Number (%)	Events
Total number of subjects w SAEs	86 (81.9%)	515
Infections and Infestations	73 (69.5%)	257
Device-related infection	45 (42.9%)	115
Pneumonia	8 (7.6%)	8
Viral upper respiratory infection	6 (5.7%)	6
Respiratory, thoracic and mediastinal disorders	39 (37.1%)	72
Respiratory failure	18 (17.1%)	22
Hypoxia	15 (14.3%)	18
Respiratory distress	6 (5.7%)	8
Gastrointestinal disorders	22 (21.0%)	27
Diarrhoea	8 (7.6%)	9
Blood and lymphatic system disorders	20 (19.0%)	32
Thrombocytopenia	8 (7.6%)	10
Neutropenia	6 (5.7%)	6
General disorders and administration site	20 (19.0%)	24
Pyrexia	18 (17.1%)	21
Metabolism and nutrition disorders	16 (15.2%)	17
Nervous system disorders	13 (12.4%)	19
Immune system disorders	13 (12.4%)	16
Renal and urinary disorders	9 (8.6%)	12
Renal failure	6 (5.7%)	7
Cardiac disorders	7 (6.7%)	8

Vascular disorders	7 (6.7%)	8
Hypotension	6 (5.7%)	6
Investigations	6 (5.7%)	7

The applicant determined 67 of the 515 SAEs to be related to Rethymic's clinical program. Events were considered possibly related if they could occur from the implantation procedure, protocol required immunosuppression, or supportive care associated with the procedures. The most frequently reported treatment-related SAEs were hemolysis (8/7.6%, under the preferred terms "autoimmune hemolytic anemia," "coombs positive hemolytic anemia", "hemolysis", and "hemolytic anemia"), thrombocytopenia (6/5.7%), neutropenia (6/5.7%), cytokine release syndrome (3/2.9%), and pancreatitis (3/2.9%). There were only two cases (1.9%) each of proteinuria, renal failure, hypoxia, respiratory failure, hypothyroidism, and cytomegalovirus infection.

There were 28 fatal cases (26.7%). The time to death ranged from 0 to 480 days in subjects who died within 2 years of implantation and from 0 to 3116 days (8.5 years) in all subjects who died. The causes of death were infection (9/8.6%), complications of infection (7/6.7%), hemorrhage (5/4.8%), respiratory failure (3/2.6%) cardiorespiratory arrest from anasarca (1/1.0%), and unknown (1/1.0%). Four (3.8%) fatal cases were considered possibly related to Rethymic's clinical program (specifically, the immunosuppressive regimen); the causes of death for these cases were complications of CMV infection (2/1.9%), respiratory failure related to RSV infection (1/1.0%), and progressive EBV lymphoma resulting in intracranial bleeding (1/1.0%).

Adverse Events of Special Interest

Infections and Immunoprophylaxis

Infectious adverse events were of special interest for this clinical program as there are three possible product-related etiologies: poor immune constitution (lack of efficacy), an adverse reaction to the immunosuppressive program, or transmission from the implanted thymic tissue. Overall, there was a significant decrease in infection-related AEs, comparing the first and second 6 months post-treatment ($p < 0.001$) and first and second 12 months post-treatment ($p < 0.0001$), suggesting that should patients survive until removal of immunosuppressive agents, they would maintain immune reconstitution.

Of note, all 3 patients with a history of CMV died after their implantation procedure. Two of these cases were considered not related to the product by study investigators; the cause of death for one was enterococci bacteremia and for the other complications of prolonged ventilation. The third case was considered related as the investigator felt the use of immunosuppressive RAT-GAM could have contributed to re-activation. There were also 2 cases of CMV viremia in patients who lacked prior history of CMV. One patient completely recovered. The second case expired from respiratory complications of the CMV infection. Only the latter case was considered possibly related, as the source of the CMV infection could not be identified (presumed transmission of infection).

The applicant also considered the subject's response to live vaccines. There were 18 subjects in the clinical program who, having received all inactivated vaccines, received the MMR vaccine and reported no adverse events. One subject was reportedly healthy until she received the varicella vaccine at one year of age. Two weeks later, the subject developed cutaneous chickenpox that spread over her body. at 27 months, the subject developed granulomatous skin lesions that likely were secondary to vaccine strain rubella (as rubella was detected in her nasopharyngeal secretions on admission for treatment with RVT-802). One subject had a pre-implantation history of rubella nasopharyngeal infection which was considered related to a vaccination that occurred prior to administration of Rethymic.

Autoimmune events

The applicant noted autoimmune adverse events that could be possibly related to thymic tissue implant. One confounder was the autoimmune conditions associated with partial DiGeorge syndrome, the most common of which are cytopenias, systemic autoimmunity, particularly rheumatoid arthritis, organ specific autoimmunity, and autoimmune thyroid disease. The applicant identified the prevalence of the following autoimmune conditions within the first 2 years of implantation: thrombocytopenia (n=24, 22.9%); anemia (n=23, 21.9%); hypothyroidism (n=21, 20.0%); neutropenia, including febrile neutropenia (n=19, 18.1%); alopecia (n=11, 10.5%); hyperthyroidism/thyroiditis (n=8; 7.6%); hemolysis or hemolytic anemia (n=8; 7.6%); and autoimmune hepatitis (n=2, 1.9%). The follow AEs occurred in 1 subject (1.0%) each: albinism, Graves' disease, immune thrombocytopenic purpura, juvenile rheumatoid arthritis, minimal change glomerulonephritis, ovarian failure, and psoriasis and psoriatic arthritis.

Autologous GVHD (aGVHD) occurred in the clinical population as the lack of thymus allowed for auto-reactive T cells to escape T cell selection. Subjects with atypical phenotype of DiGeorge could have similar signs and symptoms of aGVHD and this was noted at enrollment. Atypical phenotype was defined as subjects having rash, lymphadenopathy, with $>50/\text{mm}^3$ T cells and the naive T cell count $<50/\text{mm}^3$ or $<5\%$ of the T cells. These symptoms are a subset of the known clinical manifestations of aGVHD; additional manifestations include elevated transaminases and enteritis leading to diarrhea. A total of 11 subjects have had adverse events of aGVHD or GVHD. Of these 11 subjects, 7 subjects had aGVHD prior to treatment with Rethymic. The remaining 4 subjects had GVHD secondary to maternal engraftment, cord blood donor cells, or maternal donor cells and/or thymus donor T cells in a subject with SCID. All cases of GVHD were reported as possibly related. Most events presented in the gastrointestinal tract or skin.

Lymphoproliferative Disorder

There was one case of pre-existing EBV lymphoma that led to a fatal intracranial hemorrhage. The applicant considered this death as related to the Rethymic clinical program because the fludarabine and dexamethasone treatment given to suppress rejection may have impaired the immune response and led to faster progression of the EBV lymphoma. There was another case of pre-existing EBV lymphoma who had 2 relapses and ultimately resolved after implantation.

HLA mismatch:

HLA type matching provides numerous benefits in organ transplantation including better graft function, fewer rejection episodes, longer graft survival, and reduced immunosuppression. In contrast, mismatches lead to more frequent rejection episodes and possible death of the graft, and is associated with lymphoproliferative disease. Rejection episodes usually require increased immunosuppression which, in turn, can increase the risk of infection and malignancy. Three subjects received prior hematopoietic transplants with a partial mismatch or matching of the mismatched allele. All three were alive at last follow up. All subjects were screened for anti-HLA antibodies prior to receiving Rethymic; though 8 subjects had positive HLA antibodies, no subject had antibodies to the Rethymic product they received. One of the 8 subjects died from cardiopulmonary arrest from anasarca determined to be not related to Rethymic.

Reviewer Comment:

The Division of Epidemiology (DE) agrees with the applicant's causality for all SAEs. Half (49.9%) of the SAEs were infectious, and almost all these infectious SAEs were considered not related given the subjects' baseline depleted immune status. Other unrelated SAEs were confounded by the subjects' underlying congenital and syndromic anomalies and their complications. These anomalies included hypocalcemia/hypocalcemic seizure, intraventricular hemorrhage, juvenile idiopathic arthritis, tracheal occlusion, Omenn syndrome, and rashes. Most SAEs possibly related to Rethymic's clinical program were autoimmune or related to the subject's immunosuppressive regimen. Autoimmune SAEs that were possibly T-cell mediated were hypothyroidism, lymphadenopathy, thrombocytopenia, neutropenia, Steven-Johnson syndrome, autoimmune hepatitis, autoimmune hemolysis, transverse myelitis, and graft versus host disease. Some SAEs are known AEs associated with the immune suppressive regimen, including cytokine release syndrome (associated with RATGAM), and pancreatitis and renal failure (associated with cyclosporine). Other SAEs were infection complications to which the immunosuppression contributed (most frequently device-related infection and pneumonia/viral upper respiratory infection).

No unexpected AEs were noted as occurring at concerning rates among trial participants.

6 SUMMARY OF PRIOR MARKETED EXPERIENCE

Not applicable. The product has not been previously approved or used outside of the clinical trials. It is a first-in-class product.

7 APPLICANT'S PROPOSED PHARMACOVIGILANCE PLAN

The applicant's pharmacovigilance plan (PVP) is outlined in the table below.

Table 4: Proposed Pharmacovigilance Plan from Applicant Risk Management Plan (version 3.0, dated 28 Jul 2021)

Type of Risk	Safety Concern	Planned pharmacovigilance Activity
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Identified	Infections and Immunoprophylaxis	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.1 on label • Congenital Athymia Patient Registry
Identified	Vaccine Administration and Live virus vaccines	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.8 on label • Congenital Athymia Patient Registry
Identified	CMV infection	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.5 on label • Congenital Athymia Patient Registry
Identified	Transmission of infectious diseases	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.3 on label • Congenital Athymia Patient Registry
Identified	Autologous Graft versus host disease (GVHD)	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.4 on label • Congenital Athymia Patient Registry
Identified	“HLA Typing” (Mismatch)	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.7 on label • Congenital Athymia Patient Registry
Potential	Autoimmune Disorders	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.2 on label • Congenital Athymia Patient Registry
Potential	Anti-HLA Antibodies	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.6 on label • Congenital Athymia Patient Registry
Potential	Malignancy	<ul style="list-style-type: none"> • Routine pharmacovigilance activity • Section 5.9 on label • Congenital Athymia Patient Registry

Regarding missing information, the applicant states that the important potential risks associated with RETHYMIC treatment of pediatric patients with congenital athymia have likely been identified. Though novel risks associated with RETHYMIC administration in the post-approval setting are not anticipated, the applicant believes the pharmacovigilance plan will capture new data through its post approval registry and routine passive surveillance.

The applicant proposes routine pharmacovigilance. Individual Case Safety Reports (ICSRs) from postmarketing sources (spontaneous, solicited, literature, and regulatory authorities) will be collected, investigated, and submitted to the FDA according to the timelines defined in 21 CFR 600.80. Submission of 15-day Alert reports and periodic safety reports will proceed according to the reporting requirements delineated in 21 CFR 600.80(c). The applicant label provides instructions specific to the identified and potential risks.

In addition to routine pharmacovigilance and labeling, the applicant is proposing one voluntary patient registry during the postmarketing period.

Table 3: Postmarketing Studies

Study Name	Description	Milestone Dates
Congenital Athymia Patient Registry	Observational cohort study to evaluate survival, immune reconstitution, and safety 2 years after implantation with Rethymic	Variables will be abstracted at month 0, 3, 6, 9, 12, 18, and 24.

The Congenital Athymia Patient Registry is an observational cohort study of 75 planned participants who have congenital athymia and are implanted with Rethymic. Eligible patients will be enrolled in the 30 days before or within 60 days following implantation. They will be followed for 2 years post-treatment. The primary objectives of the study are to evaluate survival and to characterize the immune reconstitution post treatment. The secondary objective is to evaluate the occurrence and timing of key adverse events of special interests (AESIs).

The variables that are collected in this observational registry will be the following:

- At baseline:
 - Demographics
 - Medical and disease history
 - Rethymic dosing
 - Height and weight
 - Immunosuppressive regimen
- At follow up:
 - Immunoglobulin replacement therapy
 - Immunizations
 - Hospitalizations
 - Immune reconstitution (flow cytometry analysis)

- Survival
- AESIs: thyroid disease, diabetes, Addison's disease, premature ovarian failure, anemia, thrombocytopenia, neutropenia, alopecia, rash persisting >2 weeks, autoimmune hepatitis, enteritis/colitis/inflammatory disease, renal disease, arthritis, malignancy

For all AESIs, the onset, duration, severity, seriousness, outcome, and attribution to Rethymic will be recorded. For infections, any identified organisms will be reported.

The primary receipt of solicited safety information will occur from the post approval registry. Enzyvant will transfer the regulatory obligations related to safety reporting for the registry to Prometrika who will gather, analyze and assess the safety data periodically. Listings of adverse events of special interests, number of hospitalizations, and estimated survival will be submitted to the FDA in the periodic reports.

8 ANALYSIS OF APPLICANT'S PHARMACOVIGILANCE PLAN

The applicant has identified all relevant safety issues suggested by the safety information in the clinical database.

Safety Issues identified in the Pharmacovigilance Plan:

- Infections and Immunoprophylaxis: The product label provides specific instructions on screening for infections and need for prophylactics. In addition to counseling patients, the applicant requires referring physicians to conduct clinical and laboratory assessments of their patients to screen for infection during the first year after treatment. These include: complete blood count with differential, serum immunoglobulins, serum chemistry, and flow cytometry. For 9 months patients are required to continue immunoglobulin replacement and pneumocystis jiroveci pneumonia prophylaxis. These immunoprophylactic measures can then be removed only once they are off immunosuppression and have normal PHA response and CD4+ T cell count. The patient registry will screen patients for infections and capture any medications taken by patients as part of its periodic report. The proposed pharmacovigilance plan for this risk is acceptable.
- Vaccine administration and live viral vaccines: The product label provides specific instructions on when to give inactivated or live vaccines. Inactivated vaccines should be administered once immunosuppressive therapies and immunoglobulin replacement are no longer needed and there are normal levels of CD4+ and CD8+ T cells. The applicant recommends giving no more than 2 inactivated vaccines per month. Regarding live vaccines, the applicant recommends postponing until the patient's immune system is reconstituted, evidenced by normal CD8 cell counts compared to CD4 cells, and no additional vaccines (live or inactivated) scheduled within 6 months of vaccination. In addition, the varicella vaccine could only be given when the total CD3 T cell count was > 10th percentile for age. The patient registry will provide further assessment and capture immunizations as part of their medical history. The proposed pharmacovigilance plan for this risk is acceptable.
- CMV infections: In addition to routine pharmacovigilance, the product label provides specific instructions on screening for CMV pre- and post-implantation.

The patient registry will capture and report CMV screening results in its periodic report. The proposed pharmacovigilance plan for this risk is acceptable.

- Transmission of infectious diseases: Donors are screened for risk of HIV, HTLV, HBV, HCV, t. pallidum, t. cruzi, WNV, TSSE, vaccinia, and Zika. Additionally, In addition to routine pharmacovigilance, the product label calls for monitoring for clinical evidence of sepsis or “communicable disease risks associated with xenotransplantation.” The patient registry will record and report screening results specifically for CMV, EBV in its periodic report. The proposed pharmacovigilance plan for this risk is acceptable.
- Autologous GVHD and GVHD: In addition to routine pharmacovigilance, the product label provides specific instructions on screening for aGVHD phenotypes during enrollment and assessments through physical examination and laboratory evaluation. T cells from the thymus donor may be detected and can be differentiated from maternal, stem cell donor, or autologous T cells with chimerism testing, allowing differentiation between GVHD (caused by allogeneic T cells from maternal engraftment, stem cell donor, or thymus donor) and aGVHD (caused by autologous T cells from the patient with congenital athymia). The patient registry will assess for and report signs and symptoms of aGVHD in its periodic report. The proposed pharmacovigilance plan for this risk is acceptable.
- HLA Typing: The product label recommends HLA matching of Rethymic to recipient alleles that were not expressed in the HCT donor. HLA matching is not required in patients who have not received a prior HCT nor a solid organ transplant. In addition to routine pharmacovigilance, the patient registry will report on any cases of mismatch and related adverse events in its periodic reports. The proposed pharmacovigilance plan for this risk is acceptable.
- Autoimmune disorders: In addition to routine pharmacovigilance, the product label provides specific instructions on screening for various autoimmune conditions. To identify cases of cytopenias and disorders of the liver, kidney, and thyroid, the applicant requires testing including CBC with differential, liver function tests, bilirubin, creatinine, urinalysis, and thyroid function tests. The patient registry will provide further assessment of autoimmune conditions as these are listed among the AESIs and report as part of its periodic report. The proposed pharmacovigilance plan for this risk is acceptable.
- Anti-HLA antibodies: All subjects are screened for anti-HLA antibodies prior to receiving Rethymic. In addition to routine pharmacovigilance, the product label provides specific instructions on screening for HLA antibodies post-implantation. The patient registry will report these findings as part of its periodic report. The proposed pharmacovigilance plan for this risk is acceptable.
- Malignancy: In addition to routine pharmacovigilance, the product label provides requires screening infant donor tissue for EBV and CMV. Additionally, recipients are screened for EBV and CMV prior to transplant, 3 months after transplant, and after potential exposures to either virus. The patient registry will provide assessment post-implantation and report it in its periodic report. The DE approves the proposed pharmacovigilance plan for this risk is acceptable.

9 DE CONCLUSIONS

The applicant PVP adequately reflects the safety concerns based on the clinical trial experience. The identified and potential risks are adequately addressed by the monitoring lab work mentioned in the product label and Congenital Athymia Patient Registry protocol; note that this is a voluntary postmarketing sponsor study.

The review team determined that a safety related postmarketing requirement (PMR) study is not needed for this product. The risks seen in the clinical trial are expected given the implantation procedure, immunosuppressive regimen, and patients' underlying conditions. Two-year follow-up in the proposed voluntary study is considered acceptable. The review team also determined that a Risk Evaluation and Mitigation Strategy (REMS) is not required for this product.

10 RECOMMENDATIONS

- Should the product be approved, DE agrees that routine pharmacovigilance is adequate to monitor the postmarketing safety for Rethymic. This includes the pharmacovigilance activities proposed by the applicant in the PVP, including adverse event reporting as required under 21 CFR 600.80, and a voluntary postmarketing registry study for 2-year follow-up, as outlined in the Risk Management plan, version 3.0, dated 28 Jul 2021. Please see the final version of the package insert submitted by the sponsor for the final agreed upon language for the label.
- The reviewed safety data do not substantiate a need for a Risk Evaluation and Mitigation Strategy (REMS), a safety postmarketing requirement (PMR) study, or a safety postmarketing commitment (PMC) study.