**09-J4000-11**

**Original Effective Date: 01/01/22**

**Reviewed: 12/11/24**

**Revised: 01/15/25**

# Subject: Allogeneic Processed Thymus Tissue–agdc (Rethymic®)

**THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.**


| | | | | | |
|---|---|---|---|---|---|
| Dosage/ Administration | Position Statement | Billing/Coding | Reimbursement | Program Exceptions | Definitions |
| Related Guidelines | Other | References | Updates | | |


## DESCRIPTION:

Allogeneic processed thymus tissue–agdc (Rethymic) was approved by the US Food and Drug Administration (FDA) in October 2021 for immune reconstitution in pediatric patients with congenital athymia. It is the first treatment to be approved for this fatal condition. The thymus tissue is obtained from donors less than or equal to 9 months of age undergoing cardiac surgery. The manufacturing process preserves the thymic epithelial cells and tissue structure and depletes most of the donor thymocytes from the tissue. The proposed mechanism of action involves the migration of recipient T cell progenitors from the bone marrow to the implanted thymus tissue, where they develop into naïve immunocompetent recipient T cells. Evidence of thymic function will be observed by the development of naïve T cells in the peripheral blood occurring at least 6 months after treatment.

Congenital athymia is an ultra-rare condition in which children are born without a thymus, causing vulnerability to life-threatening infections and immune dysregulation. The estimated incidence of congenital athymia in the US is approximately 17 to 24 infants per 4 million live births annually. The thymus is responsible for the development of mature T cells and is the only organ where thymocytes can mature, be selected, and survive to become naive T cells. T cells originate in the bone marrow as progenitor cells; however, the bone marrow does not contain the specialized tissue required for T-cell maturation. Without a functioning thymus, the inability to produce immunocompetent T cells leads to immunodeficiency manifested as increased susceptibility to infection. With only supportive care, children with congenital athymia typically do not survive beyond 2 to 3 years of age. Congenital athymia is often associated with other conditions, such as DiGeorge syndrome (a.k.a., 22q11.2 deletion syndrome); mutations in the genes *TBX1*, *CHD7* (CHARGE syndrome - coloboma, heart defects, choanal atresia, growth or mental retardation, genital hypoplasia, and ear anomalies and/or deafness), and *FOXN1* (FOXN1 deficiency); and diabetic embryopathy. These systemic conditions make the complex

treatment of congenital athymia even more complicated. Early detection of congenital athymia is critical, as the sooner it is identified, the sooner isolation, infection prevention measures, and prophylactic antimicrobials can be initiated. Newborn screening plays a crucial role in early detection. Congenital athymia is initially detected through T-cell receptor rearrangement excision circle (TREC) screening, also known as severe combined immunodeficiency (SCID) screening. TREC screening provides the first indication of an immunologic issue in an infant's T-cell development, and it is a standard part of the newborn screening panel, required in all 50 US states as of 2018. Low or undetectable TREC levels (i.e., a positive screening result) indicate the need for further testing including flow cytometry and genetic testing to confirm a diagnosis of congenital athymia.

The efficacy of Rethymic leading to FDA approval was evaluated in 10 prospective, single-center, open-label studies that enrolled a total of 105 patients, including 95 patients in the primary efficacy analysis. The demographics and baseline characteristics of the patients enrolled in the clinical studies were similar across studies. Across the efficacy population, 59% were male; 70% were White, and 22% were Black. The median age at the time of treatment was 9 months (range of 1 to 36 months). The diagnosis of congenital athymic was based on flow cytometry documenting fewer than 50 naïve T cells/$mm^3$ (CD45RA+, CD62L+) in the peripheral blood or less than 5% of total T cells being naïve in phenotype for most patients (91 of 95). In addition congenital athymia, patients also had complete DiGeorge syndrome (cDGS; also referred to as complete DiGeorge anomaly (cDGA)) if they also met at least one of the following criteria: congenital heart defect, hypoparathyroidism (or hypocalcemia requiring calcium replacement), 22q11 hemizygosity, 10p13 hemizygosity, CHARGE syndrome, or *CHD7* mutation. Across the efficacy population, 93 patients (98%) were diagnosed with cDGS, and the most common DiGeorge gene mutations or syndromic associations were chromosome 22q11.2 deletion (36 patients; 38%) and CHARGE syndrome (23 patients; 24%). There were 35 patients with missing or no identified genetic mutations. Two (2%) patients had FOXN1 deficiency, and 1 patient (1%) had a TBX variant. There were 50 (53%) patients with typical cDGS; these patients had congenital athymia with the absence of a T cell-related rash. There were 42 (44%) patients diagnosed with atypical cDGS; these patients may have had a rash, lymphadenopathy, or oligoclonal T cells. Patients who did not have congenital athymia (e.g., SCID) and patients with prior transplants, including thymus and HCT, were excluded from the efficacy analysis population. Patients with heart surgery anticipated within 4 weeks prior to, or 3 months after, the planned Rethymic treatment date, patients with human immunodeficiency virus (HIV) infection, and patients who were not considered good surgical candidates were excluded from study participation. Patients in the efficacy population received Rethymic in a single surgical procedure at a dose of 4,900 to 24,000 $mm^2$ of Rethymic per recipient body surface area (BSA) in $m^2$. Patients were assigned to receive immunosuppressive therapy prior to and/or after treatment according to their disease phenotype and pre-Rethymic phytohemagglutinin (PHA) response. No patients were retreated with Rethymic.

The Kaplan-Meier estimated survival rates were 77% (95% CI [0.670, 0.841]) at 1 year and 76% (95% CI [0.658, 0.832]) at 2 years. For patients who were alive at 1 year after treatment, the survival rate was 94% at a median follow-up of 10.7 years. Without treatment, congenital athymia is fatal in childhood. In a natural history population observed from 1991 through 2017, 49 patients diagnosed with congenital athymia received supportive care only. The 2-year survival rate was 6%, with all patients dying by 3 years of age. The most common cause of death was infection in 26 (53%) patients. Other common causes (≥10%) included support withdrawn in 7 (14%) patients, respiratory arrest in 5 (10%) patients, and cardiac arrest in 5 (10%) patients. Rethymic also significantly reduced the number of infections over

time. In the first year after treatment, the number of patients with an infection event onset 6 to ≤12 months after treatment decreased by 38% (from 63 to 39) relative to the number of patients with an infection event onset in the first 6 months post-treatment. A two-year analysis showed a decrease in both the number of patients with an infection event and the mean number of infection events per patient, with an onset in the first 12 months post-treatment as compared to 12 to ≤24 months after treatment. There was a mean difference of 2.9 events ($p<0.001$) per patient. Following Rethymic treatment., naïve CD4+ and CD8+ T cells reconstituted over the first year, with a durable increase through Year 2. Median (minimum, maximum) naïve CD4+ T cells/$mm^3$ increased from a baseline of 1 (0, 38) to values of 42 (0, 653), 212 (1, 751), and 275 (33, 858) at 6, 12, and 24 months after treatment, respectively. Median naïve CD8+ T cells/$mm^3$ increased from a baseline of 0 (0, 46) to values of 9 (0, 163), 58 (0, 304), and 86 (6, 275) at 6, 12, and 24 months after treatment, respectively. This was accompanied by functional improvements based on T cell proliferative responses to PHA.

## POSITION STATEMENT:

The implantation of allogeneic processed thymus tissue–agdc (Rethymic) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "8"):

1. The member has a confirmed diagnosis of congenital athymia **AND** the diagnosis of severe combined immunodeficiency (SCID) has been ruled out (i.e., no SCID-causing genetic defects identified) - *laboratory and/or medical record documentation of the flow cytometry and genetic testing results confirming the diagnosis must be submitted. Flow cytometry must show fewer than 50 naïve T cells/$mm^3$ (CD45RA+, CD62L+) in the peripheral blood or less than 5% of total T cells being naïve in phenotype.*
2. The member's congenital athymia diagnosis has been confirmed by and the member's treatment plan (including Rethymic implantation) and follow-up care will be under the supervision of a pediatric immunologist or other specialist with expertise in the management of congenital athymia
3. The member is currently receiving, and will continue to receive, standard of care supportive measures for congenital athymia until immune reconstitution is deemed sufficient (generally at least 9 to 12 months after Rethymic treatment) which should include the following ("a", "b", and "c") - *medical record documentation of the standard of care supportive measures implemented must be submitted*:
    a. Antimicrobial prophylaxis to prevent bacterial, fungal, and viral infections [at a minimum, this must include Pneumocystis jiroveci pneumonia (PJP) prophylaxis, usually with trimethoprim-sulfamethoxazole (TMP-SMX)]
    b. Immunoglobulin replacement therapy
    c. Strict infection control, sanitation, and isolation protocols to limit exposure to infectious pathogens
4. To decrease the risk of graft-versus-host disease (GVHD), the member will receive immunosuppressive therapy, if needed, prior to and/or after Rethymic treatment based on their disease phenotype (i.e., typical vs. atypical complete DiGeorge syndrome) and pretreatment phytohemagglutinin (PHA) response in accordance with the recommendations in the Rethymic product labeling (Tables 2 and 3). Immunosuppressive therapies most often include anti-thymocyte globulin [rabbit] (Thymoglobulin), methylprednisolone, and cyclosporine.

5. The member has been, or will be, screened for anti-HLA antibodies prior to receiving Rethymic
6. Implantation of Rethymic will be done by a qualified surgical team in a single surgical session at a qualified hospital
7. The member has not previously received thymus tissue implantation for the treatment of congenital athymia in their lifetime
8. The Rethymic implantation will not exceed a single, one-time dose (up to 22,000 $mm^2$ of Rethymic surface area per $m^2$ recipient BSA, not to exceed 42 slices) as calculated and supplied by the manufacturer

**Approval duration**: 3 months (to allow a single implantation of Rethymic)

## DOSAGE/ADMINISTRATION:

**THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.**

**FDA-approved**

- Indicated for immune reconstitution in pediatric patients with congenital athymia.
  - Limitations if Use: Allogeneic processed thymus tissue is not indicated for the treatment of patients with severe combined immunodeficiency (SCID).
- Surgical implantation of Rethymic into the quadriceps muscle should be done by a qualified surgical team in a single surgical session at a qualified hospital. Refer to the product labeling for detailed administration instructions.
- The dosage is determined by the total surface area of the Rethymic slices and the recipient's body surface area (BSA). A slice is defined as the contents on a single filter membrane (the slices are variable in size and shape). The recommended dose range is 5,000 to 22,000 $mm^2$ of Rethymic surface area per $m^2$ 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. Up to 42 cultured slices will be provided for each patient. At the time of surgery, the manufacturing personnel communicate to the surgical team the portion of the product that represents the minimum dose.

**Dose Adjustments**

- Hepatic Impairment: Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.
- Renal Impairment: Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed. However, renal impairment at baseline is considered a risk factor for death per the product labeling.

**Drug Availability**

- A single-dose unit supplied ready for use as slices of processed thymus tissue, in sterile, polystyrene dishes (drug product dishes). Each drug product dish contains up to 4 Rethymic slices, adhered to circular filter membranes on top of surgical sponges in 5 mL of medium containing fetal bovine serum. All drug product dishes are supplied in a polycarbonate container in an insulated shipping box.
- Up to 42 slices are supplied in a single-dose unit according to the dosage calculated in advance by the manufacturer for the specific patient. At the time of surgery, the manufacturing personnel communicate to the surgical team the portion of the product that represents the minimum dose. If any slices are not administered to the patient, manufacturing personnel return this tissue to the manufacturing facility and dispose of this tissue as biohazardous waste.
- Store Rethymic at room temperature in the polycarbonate container in the insulated shipping box until ready for use. Do not refrigerate, freeze, agitate, or sterilize. Use Rethymic prior to the time and date of expiration printed on the polycarbonate container.

## PRECAUTIONS:

**Boxed Warning**

- None

**Contraindications**

- None

**Precautions/Warnings**

- **Infection Control and Immunoprophylaxis**: Immune reconstitution sufficient to protect from infection is unlikely to develop prior to 6 to 12 months after treatment with Rethymic. Given the immunocompromised condition of athymic patients, follow infection control measures until the development of thymic function is established as measured through flow cytometry. This should include counseling patients and their caregivers on good handwashing practices and minimizing exposure to visitors. Monitor patients closely for signs of infection, including fever. If a fever develops, assess the patient by blood and other cultures and treat with antimicrobials as clinically indicated. Patients should be maintained on immunoglobulin replacement therapy until all of the following criteria are met:
    - No longer on immunosuppression (at least 10% of CD3+ T cells are naïve in phenotype).
    - At least 9 months post-treatment.
    - Phytohemagglutinin (PHA) response within normal limits.
    - Normal serum IgA is also desirable but not required.
- Two months after stopping immunoglobulin replacement therapy, the IgG trough level should be checked.
    - If the IgG trough level is in the normal range for age, the patient can remain off of immunoglobulin replacement.

- If the IgG trough level is lower than the normal range for age, immunoglobulin replacement therapy should be restarted and continued for a year before being retested using the above guidelines.

- Prior to and after treatment with Rethymic, patients should be maintained on Pneumocystis jiroveci pneumonia prophylaxis until all of the following criteria are met:
  - No longer on immunosuppression (at least 10% of CD3+ T cells are naïve in phenotype).
  - At least 9 months post-treatment.
  - PHA response within normal limits.
  - CD4+ T cell count > 200 cells/mm3.
- **Graft versus Host Disease**: In clinical studies, GVHD occurred in 11 (10%) treated patients of whom 6 (55%) died. Rethymic may cause or exacerbate pre-existing GVHD. Risk factors for GVHD include atypical complete DiGeorge anomaly phenotype, prior HCT and maternal engraftment. GVHD may manifest as fever, rash, lymphadenopathy, elevated bilirubin and liver enzymes, enteritis, and/or diarrhea. Patients with elevated baseline T cell proliferative response to PHA > 5,000 cpm or > 20-fold over background should receive immunosuppressive therapies to decrease the risk of GVHD (see Tables 2 and 3 in the product labeling). Development of GVHD symptoms should be closely monitored and promptly treated.
- **Autoimmune Disorders**: Thirty-seven patients (35%) in the clinical program experienced autoimmune-related adverse reactions (refer to the product label for the full list of reactions). The onset of autoimmune related events ranged from the three days before the surgical implantation procedure until 16 years post-treatment. Most events occurred within the first year after treatment. Monitor complete blood counts with differential weekly for the first 2 months post-treatment and then monthly through 12 months post-treatment. Liver enzymes including aspartate aminotransferase and alanine aminotransferase, serum creatinine levels, and urinalysis should be performed monthly for 3 months and then every 3 months through 12 months post-treatment. Thyroid function studies should be performed prior to treatment and then at 6 months and 12 months post-treatment. After 12 months, testing should be performed annually.
- **Renal Impairment**: Ten patients with renal impairment (elevated serum creatinine at baseline) were treated in studies with Rethymic. Five of these patients died within 1 year and a sixth patient died 3 years after treatment. Renal impairment at baseline is considered a risk factor for death.
- **Cytomegalovirus Infection**: In clinical studies, 3 out of 4 patients with preexisting CMV infection prior to treatment with Rethymic died. The benefits/risks of treatment should be considered prior to treating patients with pre-existing CMV infection.
- **Malignancy**: Because of the underlying immune deficiency, patients who receive Rethymic may be at risk of developing post-treatment lymphoproliferative disorder. The infant tissue donor is screened for Epstein-Barr virus (EBV) and cytomegalovirus (CMV), but patients should be tested for EBV and CMV using PCR prior to and 3 months following treatment with Rethymic, or after any exposure to or suspected infection with CMV or EBV.
- **Transmission of Serious Infections and Transmissible Infectious Diseases**: Transmission of infectious disease may occur because Rethymic is derived from human tissue. Disease may be caused by known or unknown infectious agents. Donors are screened for increased risk of

infection from various pathogens (refer to product labeling for full list). Blood samples (from the infant tissue donor or the birth mother, as applicable) are tested for various pathogens as well.

- **Vaccine Administration**: Immunizations should not be administered in patients who have received Rethymic until immune-function criteria have been met (refer to the product labeling for specific criteria).
- **Anti-HLA Antibodies**: All patients should be screened for anti-HLA antibodies prior to receiving Rethymic. Patients testing positive for anti-HLA antibodies should receive Rethymic from a donor who does not express those HLA alleles.
- **HLA Typing**: HLA matching is required in patients who have received a prior hematopoietic cell transplantation (HCT) or a solid organ transplant. Patients who have received a prior HCT are at increased risk of developing GVHD after Rethymic if the HCT donor did not fully match the recipient. To minimize this risk, HLA matching of Rethymic to recipient alleles that were not expressed in the HCT donor is recommended.

## BILLING/CODING INFORMATION:

### HCPCS Coding

| | |
|---|---|
| J3590 | Unclassified biologics |

### ICD-10 Diagnosis Codes That Support Medical Necessity

| | |
|---|---|
| Q89.8 | Other specified congenital malformations |

## REIMBURSEMENT INFORMATION:

Refer to section entitled.

## PROGRAM EXCEPTIONS:

**Federal Employee Program (FEP):** Follow FEP guidelines.

**State Account Organization (SAO):** Follow SAO guidelines.

**Medicare Part D:** Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

**Medicare Advantage:** No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline review date.

## DEFINITIONS:

None

## RELATED GUIDELINES:

None

## OTHER:

None

## REFERENCES:


1. Clinical Pharmacology powered by ClinicalKey [Internet]. Tampa, FL: Elsevier.; 2021. Available at: https://www.clinicalkey.com/pharmacology/. Accessed 11/22/24.
2. Collins C, Kim-Chang JJ, Hsieh E, Silber A, O'Hara M, Kulke S, Cooper MA. Economic burden of congenital athymia in the United States for patients receiving supportive care during the first 3 years of life. J Med Econ. 2021 Jan-Dec;24(1):962-971.
3. Collins C, Sharpe E, Silber A, et al. Congenital Athymia: Genetic Etiologies, Clinical Manifestations, Diagnosis, and Treatment. J Clin Immunol. 2021 Jul;41(5):881-895. Epub 2021 May 13.
4. DRUGDEX System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically. Accessed 11/22/24.
5. Gupton SE, McCarthy EA, Markert ML. Care of children with DiGeorge before and after cultured thymus tissue implantation. J Clin Immunol. 2021;41(5):896-905.
6. Hsieh EWY, Kim-Chang JJ, Kulke S, et al. Defining the clinical, emotional, social, and financial burden of congenital athymia. Adv Ther. 2021;38(8):4271-4288.
7. Markert ML, Gupton SE, McCarthy EA. Experience with cultured thymus tissue in 105 children. J Allergy Clin Immunol. 2021 Aug 3:S0091-6749(21)01056-3. Epub ahead of print.
8. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 2024 Nov 22]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.
9. Rethymic (allogenic thymocyte-depleted thymus tissue-agdc implant) [package Insert]. Marlborough, MA: Sumitomo Pharma America, Inc. July 2023.


## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 12/11/24.

## GUIDELINE UPDATE INFORMATION:

| | |
|---|---|
| 01/01/22 | New Medical Coverage Guideline. |
| 01/15/24 | Review and revision to guidelines consisting of updating the references. |
| 01/15/25 | Review and revision to guidelines consisting of updating the references. |