Clinical Policy: Allogenic Processed Thymus Tissue-agdc (Rethymic)

Reference Number: PA.CP.PHAR.563
Effective Date: 01/2023
Last Review Date: 01/2024

Description
Allogenic processed thymus tissue-agdc (Rethymic®) is a regenerative tissue-based therapy.

FDA Approved Indication(s)
Rethymic is indicated for immune reconstitution in pediatric patients with congenital athymia.

Limitation(s) of use: Rethymic is not indicated for the treatment of patients with severe combined immunodeficiency (SCID).

Policy/Criteria
Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of PA Health & Wellness® that Rethymic is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Congenital Athymia (must meet all)**:**

1. Diagnosis of congenital athymia;
2. Diagnosis is confirmed by $CD3^+$ $CD4^+$ $CD45RA^+$ $CD62L^+$ T-cell count < $50/mm^3$ or < 5% of the total T-cell count based on flow cytometry;
3. One of the following (a or b):
   a. Absence of genetic defects associated with SCID (*see Appendix E*);
   b. At least one of the following to define complete DiGeorge syndrome (cDGS): congenital heart defect, hypoparathyroidism/hypocalcemia, 22q11 hemizygosity, 10p13 hemizygosity, CHARGE syndrome (*see Appendix D*), or CDXH7 mutation;
4. Prescribed by or in consultation with a pediatric immunologist;
5. Age ≤ 18 years;
6. Member does not have preexisting CMV infection (e.g., > 500 copies/mL in the blood by PCR on two consecutive assays), if member does have preexisting CMV infection the risks vs benefits were considered;
7. Documentation of anti-human leukocyte antigen (HLA) antibody screening prior to treatment;
8. If positive for anti-HLA antibodies, member must receive Rethymic from a donor who does not express HLA alleles;
9. If member previously received a hematopoietic cell transplantation (HCT) or a solid organ transplant, both of the following (a and b):
   a. HLA matching is required;
   b. Member must receive Rethymic HLA matched to recipient alleles that were not expressed in the HCT donor;

10. Rethymic is prescribed in combination with immunosuppressive therapy based on disease phenotype and phytohemagglutinin (PHA) levels *(see Appendix F)*;
11. Request meets both of the following (a and b);
    a. Dose does not exceed 22,000 mm^2 of Rethymic /m^2 recipient body surface area (up to 42 Rethymic slices);
    b. Request is for a one-time application only.

Approval duration: 1 month (one time application only per lifetime)

B. Other diagnoses/indications

1. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

II. Continued Therapy

A. Congenital Athymia

1. Continued therapy will not be authorized as Rethymic is indicated to be dosed one time only.

Approval duration: Not applicable

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. Currently receiving medication via PA Health & Wellness benefit and documentation supports positive response to therapy or the Continuity of Care policy (PA.LTSS.PHAR.01) applies.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to the off-label use policy if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): PA.CP.PMN.53

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – PA.CP.PMN.53.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ATG-R: anti-thymocyte globulin (rabbit)
cDGS: complete DiGeorge syndrome
CMV: cytomegalovirus
CPM: counts per minute
FDA: Food and Drug Administration
HCT: hematopoietic cell transplantation
HLA: human leukocyte antigens
MMF: mycophenylate mofetil
PHA: phytohemagglutinin
SCID: severe combined immunodeficiency

Appendix B: Therapeutic Alternatives

Not applicable

Appendix C: Contraindications/Boxed Warnings

None reported

Appendix D: General information

- Congenital athymia is a rare condition characterized by the absence of a thymus at birth resulting in profound immunodeficiency and immune dysregulation. Children with congenital athymia generally do not survive beyond early childhood.
- CHARGE syndrome is a disorder that affects many areas of the body. CHARGE is an abbreviation for several of the features common in the disorder: coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities.

Appendix E: SCID Defects

Disease	Genetic Defect
γc deficiency (X-linked SCID, CD132 deficiency	IL2RG
JAK3 deficiency	JAK3
IL7Rα deficiency	IL7R
CD45 deficiency	PTPRC
CD3δ deficiency	CD3D
CD3ε deficiency	CD3E
CD3ζ deficiency	CD3Z
Coronin-1A deficiency	CORO1A
LAT deficiency	LAT
RAG deficiency	RAG 1, RAG 2
DCLRE1C (Artemis) deficiency	DCLRE1C
DNA PKcs deficiency	PRKDC
Cernunnos/XLF deficiency	NHEJ1
DNA ligase IV deficiency	LIG4
Adenosine deaminase (ADA) deficiency	ADA
AK2 defect	AK2
Activated RAC2 defect	RAC2

Appendix F: Treatment Assignment to Immunosuppression

Complete DiGeorge Anomaly Phenotype	PHA Response	Immunosuppression Used with Rethymic
Typical	< 5,000 cpm or < 20-fold response to PHA over background	None
Typical	> 5,000 cpm and < 50,000 cpm or evidence of maternal engraftment	ATG-R Methylprednisolone
Typical	> 50,000 cpm	ATG-R Methylprednisolone Cyclosporine
Atypical	< 40,000 cpm on immunosuppression or < 75,000 cpm when not on immunosuppression	ATG-R Methylprednisolone Cyclosporine
Atypical	≥40,000 cpm on immunosuppression or ≥75,000 cpm when not on	ATG-R Methylprednisolone Cyclosporine

Complete DiGeorge Anomaly Phenotype	PHA Response	Immunosuppression Used with Rethymic
	immunosuppression or evidence of maternal engraftment	Basiliximab MMF

V. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Congenital athymia	5,000 to 22,000 mm^2 of Rethymic surface area per m^2 of recipient BSA as a single surgical procedure	22,000 mm^2 of Rethymic surface area/m^2 recipient BSA; up to 42 cultured Rethymic slices

VI. Product Availability

Slices of processed tissue with varying thickness and shape; each drug product dish contains up to 4 Rethymic slices

VII. References

1. Rethymic Prescribing Information. Cambridge, MA: Enzyvant Therapeutics, Inc; July 2023. Available at: https://enzyvant.com/wp-content/uploads/2021/10/prescribing-information.pdf. Accessed October 31, 2023.
2. Collins C, Sharpe E, Silber A, Kulke S, Hsieh EWY. Congenital Athymia: Genetic Etiologies, Clinical Manifestations, Diagnosis, and Treatment. J Clin Immunol. 2021;41(5):881-895.
3. Markert ML, Gupton SE, McCarthy EA. Experience with cultured thymus tissue in 105 children [published online ahead of print, 2021 Aug 3]. J Allergy Clin Immunol. 2021;S0091-6749(21)01056-3. doi:10.1016/j.jaci.2021.06.028.
4. Tangye SG, Al-Herz W, Bousfiha A, et al. Human Inborn Errors of Immunity: 2019 Update on the Classification from the International Union of Immunological Societies Expert Committee [published correction appears in J Clin Immunol. 2020 Feb 22;:]. J Clin Immunol. 2020;40(1):24-64. doi:10.1007/s10875-019-00737-x.

Coding Implications

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J3590	Unclassified biologics
C9399	Unclassified drugs or biologicals

Reviews, Revisions, and Approvals	Date
Policy created	01/2023
1Q 2024 annual review: no significant changes; references reviewed and updated.	01/2024