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

Reference Number: CP.PHAR.563
Effective Date: 03.01.22
Last Review Date: 02.25
Line of Business: Commercial, HIM, Medicaid

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 health plans affiliated with Centene Corporation® 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 *CHD7* 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);
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)

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

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 – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

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
PCR: polymerase chain reaction
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*
SLP76 deficiency	*LCP2*
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 immunosuppression or evidence of maternal engraftment	ATG-R Methylprednisolone Cyclosporine 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://www.rethymic.com/RETHYMIC_Prescribing_Information_English.pdf. Accessed November 20, 2024.
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: 2022 Update on the Classification from the International Union of Immunological Societies Expert Committee. J Clin Immunol. 2022;42(7):1473-1507.

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	P&T Approval Date
Policy created	11.15.21	02.22
Updated HCPCS codes.	05.05.22	
1Q 2023 annual review: no significant changes; clarified PCR assay is an example of CMV infection diagnosis with the addition of "e.g."; references reviewed and updated.	10.27.22	02.23
1Q 2024 annual review: no significant changes; references reviewed and updated.	11.01.23	02.24
1Q 2025 annual review: no significant changes; corrected "CDXH7" mutation to "CHD7"; references reviewed and updated.	11.20.24	02.25

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program

approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.