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Section:	Prescription Drugs	**Effective Date:**	January 1, 2024
Subsection:	Hematological Agents	**Original Policy Date:**	November 5, 2021
Subject:	Rethymic	**Page:**	1 of 5

Last Review Date: December 8, 2023

Rethymic

Description

Rethymic (allogeneic processed thymus tissue-agdc)

Background
Congenital athymia is a rare condition so named, due to the absence of a functioning thymus at birth. The thymus plays a critical role in immune system development. T cell precursor cells mature in the subcapsular tissue of the thymus's cortex. Patients with congenital athymia therefore, have profound immunodeficiency and suffer from frequent infections, a propensity for opportunistic infection, and frequently develop autologous graft-versus-host disease (aGVHD). aGVHD is often due to auto-reactive T cells found in these patients because the thymus is absent or otherwise unable to perform T cell selection (1).

Rethymic consists of up to 42 yellow to brown slices of processed thymus tissue. The tissue is implanted into the patient's muscle in a single surgical procedure. The implanted tissue is proposed to act as a natural thymus and reconstitute patient immunity through the T cell maturation process. Thymic function is generally not observed until 6 to 12 months after treatment (1).

Regulatory Status
FDA-approved indication: Rethymic is indicated for immune reconstitution in pediatric patients with congenital athymia (1).

Limitations of Use: (1)

- Rethymic is not indicated for the treatment of patients with severe combined immunodeficiency (SCID).

Rethymic has warnings regarding the possible development of lymphoproliferative disorders (blood cancers), autoimmune disorders, and graft-versus-host disease. Patients should be monitored for the development of these conditions (1).

Patients are unlikely to produce an immune response sufficient to prevent or combat infection for 6 to 12 months. Infection control measures should be implemented, and vaccinations withheld until thymic function can be established and immune function-criteria have been met (1).

Patients that receive Rethymic are also at risk of infectious disease. Rethymic is made using human tissue and cultured using porcine and bovine-derived ingredients. The risk of transmission of known or unknown disease cannot be completely ruled out even with extensive testing (1).

The safety and effectiveness of Rethymic in adult patients 18 years and older have not been established (1).

Related policies

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Rethymic may be considered **medically necessary** if the conditions indicated below are met.

Rethymic may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 17 years of age or younger

Diagnosis

Patient must have the following:

1. Congenital athymia
    a. 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
    b. Patient has **ONE** of the following:
        i. Diagnosis of *FOXN1* deficiency
        ii. A *TBX* variant
        iii. Individual has complete DiGeorge syndrome [cDGS; also referred to as complete DiGeorge anomaly (cDGA)] defined as the individual meeting at least **ONE** of the following criteria:
            1. Congenital heart defect
            2. Hypoparathyroidism (or hypercalcemia requiring calcium replacement)
            3. 22q11 hemizygosity
            4. 10p13 hemizygosity
            5. CHARGE (coloboma, heart defect, choanal atresia, growth and development retardation, genital hypoplasia, ear defects including deafness) Syndrome
            6. *CHD7* mutation

AND ALL of the following:

1. **NO** severe combined immunodeficiency (SCID)
2. Documentation of anti-HLA antibody screening
3. Prescriber agrees to withhold immunizations until immune function is established
4. Benefits and risks of treatment have been evaluated in patients with pre-existing CMV infection or who have renal impairment
5. Documentation that patient is HIV negative
6. Patient is not anticipating heart surgery within 4 weeks prior to, or 3 months after, the planned Rethymic treatment date

Prior–Approval *Renewal* Requirements

None

Policy Guidelines

Pre–PA Allowance

None

Prior–Approval Limits

Quantity 1 surgical implantation per lifetime

Prior–Approval *Renewal* Limits

None

Rationale

Summary

Rethymic is allogeneic thymic tissue harvested during cardiac procedures and cultured for implantation in congenitally athymic pediatric patients. Patients lacking a thymus suffer profound immunodeficiency and are unable to mount sufficient immune response due to a lack of immunocompetent T cells. Immature T cells migrate to the thymus to undergo the maturation process. Patients typically develop thymic activity 6 to 12 months after implantation. Patients should be monitored for the development of graft-versus-host disease, autoimmune disorders, and lymphoproliferative disorder. Safety and effectiveness in adult patients have not been established (1).

Prior approval is required to ensure the safe, clinically appropriate, and cost-effective use of Rethymic while maintaining optimal therapeutic outcomes.

References

1. Rethymic [package insert]. Cambridge, MA: Enzyvant Therapeutics, Inc.; October 2021.

Policy History

Date	Action

November 2021	Addition to PA
December 2021	Annual review
September 2022	Annual review
December 2022	Revised to align with Association policy: added required documentation of congenital athymia via flow cytometry or peripheral blood smear and a diagnosis of FOX1 deficiency or complete DiGeorge syndrome. Added requirement of anti-HLA antibody screening, agreement to advise regarding risks and benefits in CMV positive patients, documentation that patient is HIV negative, and patient is not anticipating heart surgery within 4 weeks prior to operation, or 3 months after Rethymic procedure. Removed agreement to monitor for blood cancer, GVHD, and autoimmune disorders
March 2023	Annual review
October 2023	BCBSA policy alignment: added TBX gene variant as evidence of congenital athymia and revised to FOXN1 deficiency
December 2023	Annual review

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 8, 2023 and is effective on January 1, 2024.