



Louisiana

allogeneic thymocyte-depleted thymus tissue-agdc (Rethymic®)

Policy # 00781

Original Effective Date: 04/11/2022

Current Effective Date: 04/11/2022

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider allogeneic thymocyte-depleted thymus tissue-agdc (Rethymic®)† for the treatment of congenital athymia to be **eligible for coverage**.**

Patient Selection Criteria

Coverage eligibility for the use of allogeneic thymocyte-depleted thymus tissue-agdc (Rethymic) will be considered when all of the following patient selection criteria are met:

- Patient has a diagnosis of congenital athymia confirmed by a pediatric immunologist; AND
- Patient does NOT have a diagnosis of severe combined immunodeficiency (SCID); AND
- Diagnosis of congenital athymia has been confirmed with documentation of the following:
 - Flow cytometry results demonstrating fewer than 50 naïve T-cells/mm³ (CD45RA⁺, CD62L⁺) in the peripheral blood or less than 5% of total T-cells being naïve in phenotype; AND
 - One of the following:
 - Genetic testing confirms 22q11.2 deletion; OR
 - Hematopoietic Stem Cells (HSCs) successfully differentiate using artificial thymic organoid (ATO) system test; OR
 - Patient has syndromic comorbidities (e.g., palatal anomalies, cardiac abnormalities, hypocalcemia, hearing loss, coloboma, etc.) associated with congenital athymia; AND

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- Patient is younger than 18 years of age; AND
- Patient has documentation of screening for anti-HLA antibodies; AND
- Medical record documentation confirms that the patient does not have pre-existing cytomegalovirus (CMV) infection or human immunodeficiency virus (HIV) infection; AND
(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)
- Patient has not previously been treated with Rethymic.
(Note: This specific patient criterion is an additional Company requirement for coverage eligibility and will be denied as not medically necessary** if not met)

Note: The medical records submitted for review should document that all medical necessity criteria are met.

When Services Are Considered Not Medically Necessary

Based on review of available data, the Company considers the use of allogeneic thymocyte-depleted thymus tissue-agdc (Rethymic) in patients with pre-existing CMV or HIV infection or who have previously been treated with Rethymic to be **not medically necessary**.**

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of allogeneic thymocyte-depleted thymus tissue-agdc (Rethymic) when patient selection criteria are not met (except those denoted above as **not medically necessary****) to be **investigational**.*

Background/Overview

Rethymic is a product derived from donor thymus tissue that is surgically implanted into pediatric patients with congenital athymia to restore immune function. The dosage is determined by the total surface area of the Rethymic slices and recipient body surface area (BSA) and is calculated and adjusted by the manufacturer. It is important to note that it takes 6-12 months after treatment with

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Rethymic for immune reconstitution to occur. Thus, patients must still follow infection control precautions and delay immunizations until immune function criteria have been met.

Congenital athymia is an ultra-rare condition with an incidence of approximately 17-24 live births per year in the United States. Patients with this condition are born without a thymus causing them to have profound immunodeficiency. Without treatment, these patients typically die from infections or autoimmune symptoms by 2 or 3 years of age. The thymus controls the development and maturation of T-lymphocytes (also called T-cells), which are essential for protection against infections. Without a thymus gland, T-cell progenitors from the bone marrow are unable to develop into naïve T-cells. This condition often occurs in babies who have certain genetic problems, especially DiGeorge syndrome or 22q11.2 deletion syndrome. In fact, the term congenital athymia was previously used interchangeably with complete DiGeorge anomaly or DiGeorge syndrome. However, current research indicates that there are distinct genetic and nongenetic conditions associated with congenital athymia. Other genetic conditions associated with congenital athymia include coloboma, heart defects, atresia choanae, retardation of growth and development, genital hypoplasia, and ear anomalies/deafness (CHARGE syndrome), as well as forkhead box protein N1 (FOXP1) deficiency. Nongenetic environmental factors (e.g., maternal diabetes; exposure to alcohol, retinoids, or bis-dichloroacetylamine) have also been associated with congenital athymia.

Congenital athymia is sometimes mistaken for severe combined immunodeficiency (SCID); patients with either disorder present with very low T-cell counts. Both congenital athymia and SCID are primary immunodeficiency disorders, but they are 2 separate conditions. SCID is caused by a dysfunction of hematopoietic stem cells of the bone marrow, whereas congenital athymia is associated with a dysfunction or absence of the thymus. These conditions can be differentiated by flow cytometry results, genetic testing for genes associated with either condition, or testing of hematopoietic stem cells using an artificial thymic organoid (ATO) system.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Rethymic was approved in October 2021 for immune reconstitution in pediatric patients with congenital athymia.

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Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

The efficacy of Rethymic 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 median (range) age at the time of treatment was 9 months (1-36). The diagnosis of congenital athymia was based on flow cytometry documenting fewer than 50 naïve T cells/mm³ (CD45RA⁺, CD62L⁺) in the peripheral blood or less than 5% of total T cells being naïve in phenotype in 91/95 patients (range 0-98 naïve T cells/mm³). In addition to congenital athymia, patients also had complete DiGeorge syndrome (cDGS) if they also met at least one of the following criteria: congenital heart defect, hypoparathyroidism, 22q11 hemizygoty, 10p13 hemizygoty, CHARGE (coloboma, heart defect, choanal atresia, growth and development retardation, genital hypoplasia, ear defects including deafness) syndrome, or CHD7 mutation. Across the efficacy population, 93 patients (98%) were diagnosed with cDGS. 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. Additionally, patients with heart surgery anticipated within 4 weeks prior to, or 3 months after, the planned Rethymic treatment date, patients with 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 mm² of Rethymic per recipient body surface area (BSA) in m². 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 with Rethymic, the survival rate was 94% at a median follow-up of 10.7 years.

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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.

Rethymic significantly reduced the number of infections over time. In the first year after treatment with Rethymic, 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.

References

1. Rethymic [package insert]. Enzyvant Therapeutics, Inc. Cambridge, MA. Updated October 2021.
2. Rethymic (allogeneic processed thymus tissue-agdc) New Drug Review. IPD Analytics. Updated October, 2021.

Policy History

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03/03/2022 Medical Policy Committee review

03/09/2022 Medical Policy Implementation Committee approval. New policy.

Next Scheduled Review Date: 03/2023

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)†, copyright 2021 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	NA
HCPCS	C9399, J3490, J3590
ICD-10 Diagnosis	Q89.8, D82.1, E32.9

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or

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diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

****Medically Necessary (or “Medical Necessity”)** - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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