VENTURA COUNTY
HEALTH CARE PLAN

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Enzyme Replacement Therapy – Adagen Utilization Management Medical Policy
- Adagen® (pegademase bovine intramuscular injection – Leadiant [obsolete 6/30/2019])

REVIEW DATE: 11/10/2021

OVERVIEW

Adagen is a modified enzyme used for enzyme replacement therapy (ERT) for the **treatment of severe combined immunodeficiency disease associated with a deficiency of adenosine deaminase (ADA-SCID).**[1] It is recommended for use in infants from birth or in children at any age at the time of diagnosis.

Disease Overview

ADA-SCID is an ultra-rare, autosomal recessive genetic disorder of purine metabolism affecting lymphocyte development, viability, and function.[1,2] It is estimated to occur in 1:200,000 to 1:1,000,000 live births. ADA is a purine salvage enzyme which metabolizes deoxyadenosine (dAdo) and adenosine (Ado) into deoxyinosine and inosine, respectively.[3] When ADA is deficient, dAdo accumulates in intracellular and extracellular compartments, along with its metabolite, deoxyadenosinetriphosphate (dATP). The buildup of both dAdo and dATP negatively impacts lymphocyte development and function by impeding DNA replication and repair, inducing apoptosis, and inhibiting lymphocyte activation.

There are a variety of phenotypes of ADA deficiency; ADA-SCID is the most severe and typically diagnosed before 1 year of age.[2] Infants with typical ADA-SCID have failure to thrive and opportunistic infections associated with marked depletion of B, T, and NK lymphocytes. Manifestations include persistent diarrhea, extensive dermatitis, recurrent pneumonia, and other life-threatening illnesses caused by opportunistic infections. Growth failure and other physical manifestations, including hepatic and neurologic abnormalities, may also be present. Without treatment, patients with ADA-SCID rarely survive beyond 1 to 2 years of age.

Guidelines

According to a consensus statement for management of ADA-SCID (2018), diagnosis is usually established by demonstrating absent or very low (< 1 % of normal) ADA catalytic activity, accompanied by elevated Ado or dAdo in plasma, urine, or dried blood spots.[4] This should be followed by genetic testing to confirm bi-allelic mutations in the *ADA* gene. ERT is recommended by the consensus panel for all patients newly diagnosed with ADA-SCID as an immediate stabilizing measure. The ideal duration of ERT has not been established. The consensus recommends that most patients use ERT as a "bridge" for a few months to approximately 2 years prior to undergoing curative therapy with a hematopoietic stem cell transplant (HSCT) or hematopoietic stem cell gene therapy. Long-term use of ERT has declined in the past 30 years and has not been systematically studied. Lymphocyte counts and function may deteriorate over time, contributing to increased risk of infections and malignancy. Therefore, ERT longer than 5 to 8 years should be avoided and employed on a continuous basis only when neither HSCT nor gene therapy have been available or effective. The consensus also suggests ERT use for patients with later-onset phenotypes who may not be ideal candidates for curative processes.

Dosing Considerations

Adagen is generally administered once every 7 days as an intramuscular injection.[1] The usual maintenance dose is 20 units/kg per week, although further increases may be necessary. A maximum single dose of 30 units/kg per week should not be exceeded. If a weekly dose greater than 30 units/kg is required, multiple injections would be needed. The optimal dosage and schedule of administration should be established for each patient based on monitoring of plasma ADA levels and biochemical markers of ADA deficiency. The dosing provided in this policy is expected to be adequate for the majority of patients; exceptions will be reviewed on a case-by-case basis by a clinician.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Adagen. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Adagen, approval requires it to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Adagen is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID).** Approve for 1 year if the patient meets the following criteria (A and B):
   - **A)** Patient has a diagnosis of ADA-SCID confirmed by one of the following criteria (i or ii):
     - **i.** At baseline (i.e., prior to initiating enzyme replacement therapy), the patient has had absent or very low (< 1% of normal) adenosine deaminase (ADA) catalytic activity; OR
     - **ii.** Patient has had molecular genetic testing confirming bi-allelic mutations in the *ADA* gene; AND
   - **B)** The medication is prescribed by or in consultation with an immunologist, hematologist/oncologist, or physician that specializes in ADA-SCID or related disorders.

   Dosing. Approve up to a maximum dose of 30 units/kg via intramuscular injection, not more frequently than twice weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Adagen is not recommended in the following situations:

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Adagen® [prescribing information]. Gaithersburg, MD: Leadiant Biosciences; November 2017.
2. Hershfield M. GeneReviews [Internet]. Updated March 16, 2017. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1483/. Accessed on November 5, 2021.
3. Gaspar HB, Aiuti A, Porta F, et al. How I treat ADA deficiency. *Blood*. 2009;114:3524-3532.
4. Kohn DB, Hershfield MS, Puck JM, et al. Consensus approach for the management of severe combined immune deficiency caused by adenosine deaminase deficiency. *J Allergy Clin Immunol*. 2019;143(3):852-863.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	No criteria changes.	11/11/2020
Annual Revision	No criteria changes.	11/10/2021