

POLICY: Enzyme Replacement Therapy – Adagen® (pegademase bovine injection for intramuscular use
– Leadiant [obsolete 6/30/2019])

DATE REVIEWED: 11/20/2019

OVERVIEW

Adagen is a modified enzyme used for enzyme replacement therapy for the treatment of severe combined immunodeficiency disease (SCID) 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.

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.

Guidelines

A consensus statement for management of ADA-SCID was recently updated (2018).⁴ 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. This should be followed by genetic testing to confirm bi-allelic mutations in the *ADA* gene. Enzyme replacement therapy (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(s). 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 1 year in duration.

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.

RECOMMENDED AUTHORIZATION CRITERIA

FDA-Approved Indications

1. **Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID).** Approve Adagen for 1 year in patients meeting both of the following criteria (A and B):
 - A) The patient has a diagnosis of ADA-SCID confirmed by one of the following (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. The 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.¹ Approve up to a maximum dose of 30 units/kg via intramuscular injection, not more frequently than twice weekly.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Adagen has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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, Inc; November 2017.
2. Hershfield M. GeneReviews [Internet]. Updated March 16, 2017. Available at: <https://www.ncbi.nlm.nih.gov/books/NBK1483/>. Accessed on November 14, 2019.
3. Gaspar HB, Aiuti A, Porta F, et al. How I treat ADA deficiency. *Blood*. 2009;114:3524-3532. Available at: <http://www.bloodjournal.org/content/114/17/3524?sso-checked=true>. Accessed on November 14, 2019.
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	Date Reviewed
New policy	--	10/31/2018
Annual revision	Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID): Dosing updated to clarify intramuscular route and to specify interval as not more frequently than twice weekly.	11/20/2019