

elapegademase-lvlr (Revcovi™)

Medicare Advantage Medical Policy #MNG-032

Original Effective Date: 01/01/2025

Current Effective Date: 01/01/2025

Applies to all products administered or underwritten by the Health Plan, 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 Health Plan may consider elapegademase-lvlr (Revcovi™)‡ for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for elapegademase-lvlr (Revcovi) will be considered when the below patient selection criteria are met:

- Initial
 - Patient has a diagnosis of adenosine deaminase severe combined immune deficiency (ADA-SCID) confirmed by one of the following:
 - 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
 - The patient has had molecular genetic testing confirming bi-allelic mutations in the *ADA* gene; AND
 - Patient has NOT undergone curative treatment with hematopoietic cell transplant (HCT) or gene therapy OR curative treatment has been unsuccessful.
- Continuation
 - Patient has a diagnosis of ADA-SCID; AND
 - Patient has received an initial authorization for Revcovi from the plan OR has provided documentation of authorization from previous Medicare Advantage plan; AND
 - Patient has experienced a positive clinical response to Revcovi (e.g., normalization of plasma ADA activity, erythrocyte deoxyadenosine nucleotide [dAXP] levels, improvement of disease symptoms, etc.).

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When Services Are Considered Not Medically Necessary

Based on review of available data, the Health Plan considers the use of elapegademase-lvlr (Revcovi) in patients who have undergone successful HCT or gene therapy or in patients who have not experienced a positive clinical response to Revcovi 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 Health Plan considers the use of elapegademase-lvlr (Revcovi) when the patient does not have a confirmed diagnosis of ADA-SCID to be **investigational**.*

Background/Overview

Revcovi is a recombinant adenosine deaminase that is indicated for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients. It replaces the missing enzyme in these patients to allow their immune system to function. There is one other adenosine deaminase replacement product, pegademase (Adagen®)‡, which is derived from bovine tissue. However, the manufacturer plans to discontinue Adagen due to potential stability issues once all patients have converted to Revcovi. Dosing for Revcovi depends on the patient's weight, prior Adagen dose, and response to therapy (measured by trough deoxyadenosine nucleotide [dAXP] level). Both products are administered as an intramuscular injection twice weekly.

ADA-SCID is an ultra-rare, autosomal recessive genetic disorder of purine metabolism affecting lymphocyte development, viability, and function. 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 and adenosine into deoxyinosine and inosine, respectively. When ADA is deficient, toxic metabolites accumulate in the extracellular compartments and prevent lymphocyte development and activation resulting in severe combined immunodeficiency (SCID). The toxic metabolites can be measured in laboratory testing in erythrocytes as total deoxyadenosine nucleotides (dAXP) and this test is often used to assess the efficacy of treatment. ADA deficiency causes about 15% of all SCID cases diagnosed in the U.S.

A consensus statement for the management of ADA-SCID was updated in 2018. Diagnosis is usually established by demonstrating absent or very low (<1% of normal) ADA catalytic activity, accompanied by elevated adenosine or deoxyadenosine in plasma, urine, or dried blood spots. This should be followed by genetic testing to confirm bi-allelic mutations in the ADA gene. Immediate management includes immunoglobulin supplementation and *Pneumocystis jirovecii* prophylaxis. Enzyme replacement therapy (Adagen, Revcovi) is recommended by the consensus panel for all patients newly diagnosed with ADA-SCID as an immediate stabilizing measure. It may be initiated prior to genetic confirmation of diagnosis. Benefits of enzyme replacement therapy include restoration of immune function and improvements in hepatocellular abnormalities, pulmonary alveolar proteinosis, and bone dysplasia. These guidelines recommend that most patients use enzyme

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replacement therapy as a “bridge” for a few months to approximately 2 years prior to undergoing curative therapy with hematopoietic cell transplant (HCT) or hematopoietic cell gene therapy. HCT from HLA-matched sibling donors or matched family donors provides long-term correction of the metabolic and immune deficiencies in ADA deficiency. Advances in supportive care have improved the outcomes of HCT. Survival rates are approximately 90% for matched sibling/family donor transplants. Additionally, these transplants do not require prior cytoreductive chemotherapy. For patients who do not have access to a matched sibling/family donor, an alternative donor may be used, but these procedures are less successful. Gene therapy is another option for curative treatment, but it is not currently approved in the US.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Revcovi was approved in October 2018 for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients.

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 safety and efficacy of Revcovi were established in two clinical studies, Study 1 and Study 2. Study 1 is an ongoing Phase 3, open-label, multicenter, single-arm, one-way crossover study conducted in the US that includes 6 patients who were previously receiving therapy with Adagen. Patients were 8-37 years of age at the start of the study and transitioned through 3 phases: an Adagen lead-in phase of at least 3 weeks, a 21 week Revcovi treatment phase, and a Revcovi maintenance phase. The starting weekly dose of Revcovi was calculated based on the last Adagen dose received in the study. Weekly Revcovi doses ranged from 0.188 mg/kg to 0.292 mg/kg. Efficacy endpoints assessed included trough dAXP level (metabolic detoxification was defined as a trough erythrocyte dAXP concentration equal to or below 0.02 mmol/L), trough plasma ADA activity (adequate trough plasma ADA activity defined as greater than or equal to 15 mmol/hr/L), and immune status. At the evaluation time point, five of six patients had reached the 21-week endpoint of the treatment phase, and three of six patients received treatment with Revcovi for over 135 weeks. These patients (except for 1 value in a patient at treatment week 47) had erythrocyte dAXP concentrations equal to or below 0.02 mmol/L. These patients all had trough plasma ADA activity equal to or above 15 mmol/hr/L at 88/89 timepoints and maintained metabolic detoxification for at least 2 years under Revcovi treatment.

Study 2 was a single-arm clinical study conducted in Japan that included 4 patients aged 3.4 months-25 years. The study included two phases, an evaluation phase consisting of a 5-week dose adjustment period and a 16-week dose maintenance period, and a continuous administration (extension) phase

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to be continued until the end of the study. Of the four patients included, 2 had received Adagen in the 4 weeks prior to the study, 1 had not received Adagen within 4 weeks prior to the study, and 1 was newly diagnosed and had never received Adagen. All patients achieved and maintained detoxification (trough dAXP ≤ 0.02 mmol/L) throughout their participation in the treatment phase of the study.

References

1. Revcovi [package insert]. Leadiant Biosciences, Inc., Gaithersburg, MD. Updated October 2018.
2. 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*. 2018 September.
3. Revcovi Drug Evaluation. Express Scripts. October 2018.
4. Revcovi (elapegademase-lv1r): for adults and pediatric patients with adenosine deaminase severe combined immune deficiency. IPD Analytics. October 2018.

Policy History

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10/15/2024 UM Committee review

Next Review: 10/2025

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2023 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.

The responsibility for the content of the Health Plan Medical Policy Coverage Guidelines is with the Health Plan and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in the Health Plan Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of the Health Plan Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

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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	No codes
HCPCS	C9399, J3490, J3590
ICD-10 Diagnosis	All related diagnoses

*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 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

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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 Health Plan 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 Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members

Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: <https://www.cms.gov/medicare-coverage-database/search.aspx>. You may wish to review the Guide to the MCD Search here: <https://www.cms.gov/medicare-coverage-database/help/mcd-bene-help.aspx>.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.