A HEALTHCARE PROFESSIONAL'S GUIDE

Revcovi®
elapegademase-lvlr
injection 1.6 mg/mL

Ashley, actual Revcovi patient

There for the journey with ADA-SCID

The only enzyme-replacement therapy (ERT) for pediatric and adult patients with adenosine deaminase severe combined immune deficiency (ADA-SCID).

Revcovi

INDICATION

Revcovi® (elapegademase-lvlr) is indicated for the treatment of adenosine deaminase severe combined immune deficiency (ADA-SCID) in pediatric and adult patients.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- Injection site bleeding in patients with thrombocytopenia: Increased risk of local bleeding in patients with thrombocytopenia; should not be used if thrombocytopenia is severe.
- Delay in improvement of immune function: Protect immune deficient patients from infections until improvement in immune function.

ADVERSE REACTIONS

The most commonly reported adverse reactions were cough (50%) and vomiting (33%).

In addition, the following post-marketing reports for the same class of enzyme replacement therapy used in the treatment of ADA-SCID may also be seen with Revcovi treatment:

- Hematologic events: hemolytic anemia, autoimmune hemolytic anemia, thrombocythemia, thrombocytopenia and autoimmune thrombocytopenia
- Dermatological events: injection site erythema, urticaria
- Lymphomas

IMPORTANT MONITORING INFORMATION

Treatment with Revcovi should be monitored by measuring trough plasma ADA activity and trough dAXP levels for maintenance of therapeutic targets. If a persistent decline in plasma ADA activity occurs, immune function and clinical status should be monitored closely, and precautions should be taken to minimize the risk of infection.

Please see Important Safety Information throughout and accompanying full Prescribing Information.

ADA-SCID: ULTRA-RARE, GENETIC—AND OFTEN FATAL IF LEFT UNTREATED[1-3]

Adenosine deaminase severe combined immune deficiency (ADA-SCID) is caused by a deficiency in the adenosine deaminase (ADA) enzyme, which is produced in all cells and is most active in lymphocytes.[1]

Patients with ADA-SCID that is left untreated often die of infection by 2 years of age.[3]

In healthy cells, ADA binds to adenosine/deoxyadenosine, a toxic metabolic byproduct, and converts it to a nontoxic byproduct.[1]

In ADA-SCID, the *ADA* gene, which produces adenosine deaminase, is defective, resulting in reduced or eliminated ADA activity.[1]

The absence of ADA leads to metabolic toxification as adenosine/deoxyadenosine builds up within the cell, compromising the immune system.[1,2]

As metabolic toxification builds, the risk of severe and recurring infections increases in patients living with ADA-SCID.[1-3]

DIAGNOSING ADA-SCID

ADA-SCID can present with either **early onset** or **delayed/late-onset** signs and symptoms.

EARLY

Early onset[3]

- Deficiencies in humoral and cellular immune function
- Low serum immunoglobulins
- Lack of lymphoid tissue
- Failure to thrive
- Opportunistic infections

LATE

Delayed/late-onset[3]

- Infections: recurrent otitis, sinusitis, and upper respiratory infections
- As disease progresses: chronic pulmonary insufficiency, cytopenias, antithyroid antibodies, allergies, and elevated serum immunoglobulin E (IgE)

Other clues

Some individuals with ADA-SCID may show reduced neutrophil counts and bone marrow abnormalities, including myeloid dysplasia and hypocellularity.[4,5]

Early detection allows for the early initiation of treatment

Newborn screening allows for timely detection of ADA-SCID.[5,6] Or, diagnosis can be confirmed by measuring ADA activity in erythrocytes and/or via molecular genetic testing.[3,5] The earlier ADA-SCID is detected and treatment initiated, the better the outcome.[5,7] **Treatment is most successful in infants who have not yet experienced serious, recurrent infections.**

Diagnosing ADA-SCID—and starting ERT early—may help prevent early death from infection.[3,5,7]

Josh, actual patient and child

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Revcovi is a PEGylated recombinant ERT indicated for the treatment of adenosine deaminase severe combined immune deficiency in pediatric and adult patients.[8]

REVCOVI DEMONSTRATED CLEAR IMPROVEMENT IN KEY MARKERS OF ADA-SCID[8]

US study description:

Phase III, open-label, multicenter, single arm, one-way crossover study to evaluate the safety, efficacy, and pharmacokinetics (PK) of Revcovi in 6 US patients with ADA-SCID who were receiving therapy with Adagen®, a legacy ERT that is no longer available for use. The study consisted of 3 phases[8]:

Adagen Lead-in At least 3 weeks › **Revcovi Treatment** Weeks 1-21 › **Maintenance** Weeks 21+

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.[8]

Endpoints included[8]:

- Primary endpoint: Metabolic detoxification through Week 21 (trough erythrocyte deoxyadenosine nucleotides [dAXP] levels ≤0.02 mmol/L)
- Secondary endpoint: Plasma ADA activity at or above 15 mmol/hr/L
- Secondary endpoint: Immune status (total lymphocyte and T-, B-, and natural killer [NK]-lymphocyte subset counts)

Improved ADA activity with Revcovi [8]

Trough plasma ADA activity values increased during the Revcovi treatment phase and were consistently >15m mmol/hr/L for all 6 patients after week 3.[9]

Mean trough plasma ADA activity[8]

34.3
± 6.6 mmol/hr/L
Revcovi (0.2 mg/kg/week)

14.2
± 5.1 mmol/hr/L
Adagen (30 U/kg/week)

- Patients achieved trough plasma ADA activity above 30 mmol/hr/L by week 5.[8]

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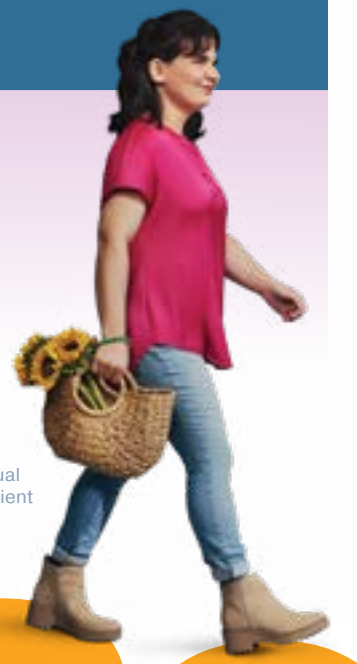
Most patients achieved metabolic detoxification with Revcovi[8]

- **Based on interim data, 5 patients (5/6) reached the protocol-defined 21-week primary endpoint[8]**
  - Three patients (3/6) receiving Revcovi for over 135 weeks achieved metabolic detoxification at most tested time points[8]
  - The other 3 patients in the study also achieved complete detoxification based on trough dAXP level[8]

Lymphocyte counts improved in some patients receiving Revcovi[8]

- **For the 3 patients (3/6) receiving Revcovi for at least 135 weeks:**
  - Total lymphocyte counts and B-, T-, and NK-lymphocyte subset counts during Revcovi treatment increased above Adagen levels observed during the lead-in phase[8]
  - Maximum increases were approximately three-fold at Weeks 60-73 for one patient, two-to-three-fold at Weeks 73-99 for one patient, and one-and-a-half-to-three-fold for the third patient at several time points.[8]* The other 3 patients in the study also showed stable or slightly increased lymphocyte counts with Revcovi as compared to Adagen lead-in phase[8,a]

A Japanese multicenter trial (4 patients) showed similar improvements in ADA activity levels, dAXP concentration, and total lymphocyte counts.[8]



Ashley, actual Revcovi patient

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* Immune function, including the ability to produce antibodies, generally improves after 2-6 months of therapy, and matures over a longer period. In general, there is a lag between the correction of the metabolic abnormalities and improved immune function. Improvement in the general clinical status of the patient may be gradual (as evidenced by improvement in various clinical parameters) but should be apparent by the end of the first year of therapy.[8]

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REVCOVI SAFETY PROFILE

- The most commonly reported adverse events (AEs) in the US study were cough and vomiting[8]
- In the Japanese study, the most common AEs were respiratory infections. One infant who had CMV pneumonitis at study entry died of CMV disease at 16 weeks[8]
- In the US study, no unexpected AEs were observed compared to patients treated with Adagen[8]
- As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity results from Study 1 and Study 2 suggest that patients who previously received Adagen may present an immunologic response to Revcovi. Therefore, monitoring for changes in ADA levels during Revcovi treatment is recommended[8]

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS

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In addition, the following post-marketing reports for the same class of enzyme replacement therapy used in the treatment of ADA-SCID may also be seen with Revcovi treatment:

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Josh, actual Revcovi patient, and partner

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ACHIEVE THERAPEUTIC DOSING THROUGH MAINTENANCE[8]

Improvement in the general clinical status of the patient may be gradual but should be apparent by the end of the first year of therapy[8]

Recommended starting dose[8]

0.4 mg/kg/wk based on ideal body weight or actual weight, whichever is greater

Divided into 2 weekly doses for a minimum of 12-24 weeks

Until immune reconstitution is achieved

Recommended maintenance dose[8]

Once immune reconstitution is achieved, dose may be gradually adjusted down to maintain trough ADA activity, trough deoxyadenosine levels and/or clinical assessment.

ADA activity >30 mmol/hr/L

Trough dAXP levels <0.02 mmol/L

To maintain adequate immune reconstitution based on the clinical assessment of the patient

Monitoring schedule[8]

Measurement	First 3 months of treatment: monitor patients **every 2 weeks**	4-12 months of treatment: monitor patients **every 1-2 months**	1 year+ of treatment: monitor patients **every 3-6 months**	Target
ADA Activity	Every 2 weeks	Every 3-6 months	Every 3-6 months	Trough plasma ADA activity ≥30 mmol/h/L*
Erythrocyte dAXP	At week 8	Every 6 months	Every 6 months	Trough dAXP levels <0.02 mmol/L
Total & Subset Lymphocytes	At weeks 4, 8, and 12	Every 1-2 months	Every 3-6 months	General improvement†

* A decrease of ADA activity below 30 mmol/hr/L might suggest noncompliance or a development of antibodies (anti-drug, anti-PEG, and neutralizing antibodies). Test for antibodies to Revcovi if pre-injection trough plasma ADA activity falls below 15 mmol/hr/L consistently. If there is a decline in ADA activity levels, monitor immune function and clinical status more closely and take precautions to minimize the risk of infection.[8]

† Immune function, including the ability to produce antibodies, generally improves after 2-6 months of therapy, and matures over a longer period. Improvement in the general clinical status of the patient may be gradual (as evidenced by improvement in various clinical parameters) but should be apparent by the end of the first year of therapy.[8]

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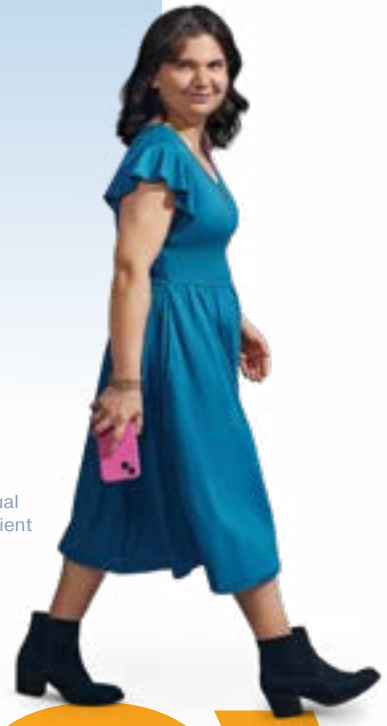
ADMINISTRATION

Revcovi is for IM injection only. Follow sterile IM administration technique guidelines appropriate to the patient's age and anatomy (choice of needle gauge and length, site of administration). Take precautions not to inject into or near an artery or nerve. Alternate the injection site periodically.[8]

Preparation of Injection and procedure instructions

- Revcovi should not be diluted nor mixed with any other drug prior to administration[8]
- Visually inspect Revcovi for particulate matter and discoloration prior to administration. Revcovi is a clear, colorless solution; discard if solution is discolored, cloudy or contains particulate matter[8]
- Do not freeze or shake. Revcovi should not be used if there are any indications that it may have been frozen. Once removed from refrigeration, allow Revcovi to equilibrate to room temperature for 30 minutes[8]
- Revcovi is to be administered using polypropylene syringes. Draw the solution from the vial with a 25-gauge needle or larger[8]
- Change the needle to a size and gauge appropriate for the patient's intramuscular administration[8]
- Revcovi should be administered immediately after syringe preparation[8]
- Any remaining medication in the vial must be discarded immediately[8]



Ashley, actual Revcovi patient

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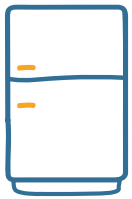
HOW SUPPLIED, AND STORAGE AND HANDLING

How supplied

- Each single-use vial of Revcovi contains 2.4 mg of elapegademase-lvlr in a 1.5 mL solution[8]
- The concentration of elapegademase-lvlr is 1.6 mg/mL[8]
- The solution is clear and colorless and contains no preservatives[8]
- The vial stopper is not made with natural rubber latex[8]



Storage & handling

- Store in the refrigerator between 2°C to 8°C (36°F to 46°F) in the original carton to protect from light[8]
- Do not freeze or shake. Do not use if there are any indications that vials were frozen[8]
- Single-dose vial; do not reuse the vial. Discard unused portions[8]
- Discard if solution is discolored, cloudy or contains particulate matter[8]

Visit chiesitotalcare.com or call 1-866-272-7078 if you have any questions.

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REVCOVI ORDERING AND SUPPORT

Ordering information

Please visit **ChiesiTotalCare.com** to access the Revcovi Order/Prescription Form and the Chiesi Total Care Enrollment Form.

Scan the QR code to download forms to your device.
Please fax completed forms to Chiesi Total Care at **1-866-272-7079**.

Josh, actual Revcovi patient

One-stop patient support

Chiesi Total Care℠ is a comprehensive support program that provides exceptional service to healthcare providers and their patients.

A single call to your dedicated Chiesi Total Care team is all it takes, and they will guide you through the process of getting a patient started on Revcovi® therapy. The Chiesi Total Care Program provides assistance to patients with or without commercial insurance, Medicaid, and Medicare. The program also offers injection support for patients who receive Revcovi injections at home.†

1. **Assess patient eligibility**
2. **Insurance assistance**
3. **Access to medication**

Revcovi

Chiesi TOTAL Care℠

Visit chiesitotalcare.com or call 1-866-272-7078 if you have any questions.

The Revcovi copay program:

Patients may pay as little as $0 for their prescription.†

Program eligibility:

- Patient must be enrolled in Chiesi Total Care. Enrollment form can be found at ChiesiTotalCare.com.
- Patient has commercial insurance and a valid prescription for a US Food and Drug Administration (FDA)-approved indication.
- Patient must be a resident of the United States or one of its territories.

† Please refer to the accompanying full Terms and Conditions for additional eligibility requirements.

Lesa, Chiesi Total Care Pharmacist

Medical information and adverse event reporting

For adverse event reporting, product complaints, or medical information inquiries:

Phone: **1-888-661-9260**
Fax: **1-866-443-3092**
Email: **us.medical@chiesi.com**

Privacy policy

Where applicable, personal information shared and processed for adverse events reporting, product orders, reimbursement support, and patient assistance is subject to Chiesi's Privacy Policy available at https://www.chiesiusa.com/privacy-policy/.

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Chiesi
global rare diseases

CHIESI GLOBAL RARE DISEASES: OUR COMMITMENT, YOUR EMPOWERMENT

Chiesi has been focused on the centrality of the patients for decades. In 2019, Chiesi created a unit specifically dedicated to the development and commercialization of products for rare diseases to further increase our focus on the patients.

We believe that no patient should be left behind, which is why we created a business unit specifically dedicated to those with rare diseases. Patients with rare diseases can encounter many difficulties, from getting a timely and accurate diagnosis, to accessing effective medical and social care, resulting in heavy burdens on patients. As such, we believe this therapeutic area to be of great importance and impact.

Years of research and innovation are in our DNA.

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References 1. Whitmore KV, Gaspar HB. Adenosine deaminase deficiency – more than just an immunodeficiency. *Front Immunol.* 2016; 7:314. doi:10.3389/fimmu.2016.00314. **2.** Sauer AV, Brigida I, Carriglio N, Aiuti A. Autoimmune dysregulation and purine metabolism in adenosine deaminase deficiency. *Front Immunol.* 2012;3:265. doi:10.3389/fimmu.2012.00265. **3.** Hershfield M. Adenosine Deaminase Deficiency. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews®*. University of Washington, Seattle; 1993-2020. Posted October 3, 2006. Updated March 16, 2017. https://www.ncbi.nlm.nih.gov/books/NBK1483/. **4.** Sokolic R, Maric I, Kesserwan C, et al. Myeloid dysplasia and bone marrow hypocellularity in adenosine deaminase-deficient severe combined immune deficiency. *Blood.* 2009;118(10):2688-2694. **5.** 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. doi:10.1016/j.jaci.2018.08.024. **6.** Kwan A, Roshini AS, Currier R, et al. Newborn screening for severe combined immunodeficiency in 11 screening programs in the United States. *JAMA*. 2020;312(7):729-738. doi:10.1001/jama.2014.9132. **7.** Gaspar HB, Aiuti A, Porta F, Candotti F, Hershfield MS, Notarangelo LD. How I treat ADA deficiency. *Blood*. 2009;114:3524-3532. **8.** Revcovi®. Prescribing information. Chiesi USA, Inc.; 2021. **9.** Dorsey MJ, Rubenstein A, Lehman H, et al. PEGylated Recombinant Adenosine Deaminase Maintains Detoxification and Lymphocyte Counts in Patient with ADA-SCID. *J Clin Immunol.* 2023 Jul;43(5):951-964. doi: 10.1007/s10875-022-01426-y. Epub 2023 Feb 25.

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NOTES

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Fax the completed forms to Chiesi Total Care staff at 1-866-272-7079.

Josh and Ashley, actual Revcovi patients

Revcovi: For your patients with ADA-SCID

See the difference Revcovi could make for your patients

The only PEGylated recombinant ERT for ADA-SCID
Revcovi is an exogenous source of ADA that does not rely on animal production.[8]

Clear improvement in markers of disease progression
Most patients receiving Revcovi achieved improved ADA activity, metabolic detoxification, and improved lymphocyte counts.[8]

Individualized dosing for individual needs
Revcovi dosing and monitoring can be customized to suit your patients' needs and schedules.[8]

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