Drug Monograph

Drug/Drug Class:	**Revcovi™ (elapegademase-lvlr) for Injection / Enzyme**
Prepared for:	MO HealthNet
Prepared by:	Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Revcovi™ is available as a 2.4 mg/1.5 mL (1.6 mg/mL) single-dose vial for injection. Leadiant Biosciences Inc., Gaithersburg, MD 20878 10/2018.
Summary of Findings:	In two prospective, open-label, single-arm, multi-center studies (N=10) Revcovi™ showed improvement over Adagen® in efficacy endpoints of dAXP Level, trough plasma ADA activity and patient immune status. The most common adverse reactions reported were cough (3/6 patients), vomiting (2/6 patients) and respiratory infections (2/4 patients). Study two also had a death due to CMV pneumonitis and respiratory failure in an infant who experienced pulmonary hemorrhage, respiratory failure and upper respiratory tract infection. Patients taking should be monitored for injection site bleeding especially in patients with thrombocytopenia as well as protected against infection until immune functions improve.

Status Recommendation:	☒ Prior Authorization (PA) Required ☐ Clinical Edit	☐ Open Access ☐ PDL
Type of PA Criteria:	☐ Increased Risk of ADE ☒ Appropriate Indications	☐ Non-Preferred Agent ☐ No PA Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [2]

Severe combined immunodeficiency (SCID) is a serious and life-threatening condition that presents as recurring infections, diarrhea, dermatitis and failure to thrive. Adenosine deaminase (ADA) deficiency is an inherited genetic disorder with damaging immune system functioning that can lead to SCID, typically in the fist few months of life. ADA-SCID has an incidence of 1 in 75,000 live births and once diagnosed, children typically die before the age of 2. This rare genetic mutation causes defects in lymphocyte development and function by causing T cell, B cell and natural killer (NK) cell deficiency. This reduction in immunity can result in severe and opportunistic infections thus making early detection vital for a chance at long-term survival. The primary treatment option for most cases is limited to blood transfusions of hematopoietic cell transplantation from an identical donor. For patients that are not candidates for transplant, or cannot find a donor, enzyme replacement therapy is the next option. There are currently two ADA replacement therapy options. Adagen® (pegademase bovine) is a first generation ADA agent that was released in 1990 and is derived from bovine intestine. Revcovi™ is a second-generation ADA agent introduced in 2018 and is not sourced from animals.

Dosage Form(s) [1]

Revcovi™ is available as a 2.4 mg/1.5 mL (1.6 mg/mL) single-dose vial for injection.

Manufacturer [1]

Leadiant Biosciences Inc., Gaithersburg, MD 20878 10/2018.

Indication(s) [1]

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

Clinical Efficacy [1] (mechanism of action/pharmacology, comparative efficacy)

Revcovi™ is an exogenous source of ADA enzyme that works to lower toxic adenosine and deoxyadenosine nucleotides levels. These nucleotides at elevated levels lead to apoptosis and a block in the differentiation of thymocytes and can cause severe T-lymphopenia. Revcovi™ works to maintain a low level of 2'-deoxyadenosine and adenosine which is vital for immune functioning and helps prevent opportunistic infections. Revcovi™ is approved for treatment of pediatric and adult patients with adenosine deaminase severe combined immune deficiency (ADA-SCID).

Pharmacokinetics:

	Revcovi™
Dose-Normalized AUC	19013 – 42400 (hr·mmol/hr/L)/(mg/kg)

Peak Plasma Time	27.2 – 72 Hours

Clinical Trials:

STUDY DESIGN	Two prospective, open-label, single-arm, multi-center studies had a total of 10 patients and took place in the US and Japan. The study efficacy endpoints were trough dAXP Level (metabolic detoxification was defined as a trough erythrocyte dAXP concentration ≥ 15 mmol/L), trough plasma ADA activity (adequate trough plasma ADA activity is defined as trough plasma ADA activity ≥ 15 mmol/L) and immune status (lymphocyte and B-, T-, and NK-lymphocyte subset counts as well as quantitative immunoglobulin [Ig] concentration [IgG, IgA, IgM]). The purpose of both studies was to evaluate the safety, efficacy and PK of Revcovi™.
INCLUSION CRITERIA	Study one (N=6) is an ongoing Phase 3 trial in 6 included patients with ADA-SCID and receiving therapy with Adagen®. Study two (N=4) is a single-arm study that included patients with ADA-SCID.
EXCLUSION CRITERIA	The study excluded patients that did not meet the inclusion criteria.
TREATMENT REGIMEN	Study one is a US Phase 3, open-label, multicenter, single-arm, one-way crossover study and consists of three phases: Adagen® Lead-in Phase (minimum of 3 weeks), the Revcovi™ Treatment Phase (weeks 1 through 21) and lastly the Revcovi™ Maintenance Phase. The starting dose of Revcovi™ was calculated based on the last Adagen® dose received in the study and ranged from 0.188 mg/kg to 0.292 mg/kg. Study two was a single-arm study conducted in Japan and included two phases: Phase one had an Evaluation, consisting of a Dose Adjustment Period (5 Weeks) and a Dose Maintenance Period (16 Weeks). Phase two is a Continuous Administration (Extension) phase which is to be continued until the end of the study. The starting dose of Revcovi™ was calculated based on the last Adagen® dose received in the study or calculated from manufacturer recommendations for Adagen®-naïve patients.
RESULTS	Study one had 5 of 6 patients reach the 21-week endpoint of the Treatment Phase and 3 of the 6 patients received treatment with Revcovi™ for over 135 weeks. These patients showed trough plasma ADA activity ≥ 15 mmol/L at 88 of 89 timepoints and maintained metabolic detoxification for at least two years with treatment. Patients achieved trough plasma ADA activity ≥ 30 mmol/L by week 5 (One patient achieved this level at Week 1) and the mean trough plasma ADA activity were 34.3 ± 6.6 mmol/hr/L and normalized at a dose of 0.2 mg/kg/week. The same patients treated with Adagen® during the Lead-in Phase had a mean

	trough plasma ADA activity of 14.2 ± 5.1 mmol.hr/L at a normalized dose of 30 U/kg/week. The study also saw increases in lymphocyte and subset counts compared to the Adagen® Lead-in Phase in three patients that completed the 21-week endpoint. For the three patients that did not reach the 21-week endpoint, observations indicate complete detoxification based on trough dAXP levels and trough plasma ADA activity along with slightly increase lymphocyte counts with Revcovi™ compared to values during the Adagen® Lead-in Phase. All four patients in the second study achieved and maintained detoxification with dAXP ≤ 0.02 mmol/L throughout the 21-week Treatment Phase. While all four patients had improvement in serum ADA activity, three patients achieved an activity level over 15 mmol/hr/L during the Dose Maintenance Period. The studies Maintenance Period had total lymphocyte counts and B-, T-, and NK-lymphocyte subset counts stable or increasing for three patients.
SAFETY	The most common adverse reactions reported were cough (3/6 patients), vomiting (2/6 patients) and respiratory infections (2/4 patients). Study two also had a death due to CMV pneumonitis and respiratory failure in an infant who experienced pulmonary hemorrhage, respiratory failure and upper respiratory tract infection.

Contraindications (1)

- Revcovi™ does not have any known contraindications.

Warnings and Precautions (1)

Revcovi™ has two warnings and precautions associated with its use:

- Injection Site Bleeding in Patients with Thrombocytopenia: Treatment with Revcovi™ should be avoided in patients with severe thrombocytopenia.
- Delay in Improvement of Immune Function: Patients should be monitored for sign and symptoms of infection until normal immune system has been achieved.

Adverse Effects (1)

Revcovi™ is an exogenous source of ADA enzyme therefore, like all other therapeutic proteins, has the potential for immunogenicity. In clinical trials of Revcovi™ suggest patients previously on Adagen® may present an immunologic response, resulting in a recommendation of ADA level monitoring during treatment. Revcovi™ also has the following postmarketing, voluntary adverse reactions reported:

- Hematologic: Hemolytic anemia, auto-immune hemolytic anemia, thrombocythemia, thrombocytopenia and autoimmune thrombocytopenia
- Dermatological: Injection site erythema, urticaria
- Lymphomas

During clinical trials, the most common side effects reported were cough (3/6 patients), vomiting (2/6 patients) and respiratory infections (2/4 patients).

Drug Interactions [1]

- While there are no direct interactions according to the drug literature, as with any enzyme therapy, interactions are possible.

Dosage and Administration [1]

Revcovi™ is an intramuscular (IM) injection with an Adagen-naïve dosage and dosing for patients transitioning from Adagen® to Revcovi™:

- The starting dose for Adagen-naïve patients is 0.4 mg/kg based on ideal body weight and divided into two doses (0.2 mg/kg twice a week). This is given until immune reconstitution is achieved (maximum of 12-24 weeks) then gradually lowered to maintain tough ADA activity over 30 mmol/hr/L, trough dAXP level under 0.02 mmol/L and/or adequate clinical assessment of immune function.
- Patients transitioning from Adagen® to Revcovi™ is based on the weekly dose Adagen®:
  - If the Adagen® dose is unknown (or weekly dose is ≤ 30 U/kg) the recommended minimum starting dose is 0.2 mg/kg once weekly.
  - If the dose is above 30 U/kg, the following equivalent weekly dose (mg/kg) should be calculated as follows:

$$\text{Revcovi™ Dose in mg/kg} = \frac{\text{Adagen® dose in U/kg}}{150}$$

Subsequent doses can be increased in increments 0.033 mg/kg weekly until trough ADA activity is above 30 mmol/hr/L, trough dAXP level is under 0.02 mmol/L and/or an adequate clinical assessment of immune function.

Ongoing dosages of Revcovi™ can vary from patient to patient and may rely on laboratory values as well as physician medical assessments. With Revcovi™ given as an IM injection, sterile technique guidelines should be followed based on patients age and anatomy to ensure complete and correct dosages are administered.

Cost

BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/VIAL*
Revcovi™	Leadiant	2.4 mg/1.5 mL	0.2 mg/kg Twice Weekly for 12-24 Weeks then lowered to maintain 30 mmol/hr/L trough ADA activity***	$9,855.99*
Adagen®	Leadiant	375 units per	10 U/kg 1st dose, 15 U/kg 2nd dose then 20	$5,259**

		1.5 mL	U/kg Weekly**	

** Wholesale Acquisition Cost*
***Maximum Allowable Cost*
****Not a complete dosing regimen. Please refer to drug information for a complete dosing schedule.*

Conclusion

Revcovi™ is a recombinant adenosine deaminase (rADA) injectable for the treatment of pediatric and adult patients with adenosine deaminase severe combined immune deficiency (ADA-SCID). In two prospective, open-label, single-arm, multi-center studies (N=10) Revcovi™ showed improvement over Adagen® in efficacy endpoints of dAXP Level, trough plasma ADA activity and patient immune status. The most common adverse reactions reported were cough (3/6 patients), vomiting (2/6 patients) and respiratory infections (2/4 patients). Study two also had a death due to CMV pneumonitis and respiratory failure in an infant who experienced pulmonary hemorrhage, respiratory failure and upper respiratory tract infection. To date, there are just two medication options for ADA-SCID. Adagen® (pegademase bovine) is a first-generation ADA agent that was released in 1990 and is derived from bovine intestine and Revcovi™ is a second-generation ADA agent introduced in 2018 and is not sourced from animals. With the non-animal sourcing, Leadiant has plans to discontinue Adagen® once patients are converted to Revcovi™ per their website. Patients taking should be monitored for injection site bleeding especially in patients with thrombocytopenia as well as protected against infection until immune functions improve.

Recommendation

The MO HealthNet Division recommends prior authorization status for this product.

References

1) Product Information: Revcovi™ (elapegademase-lvlr), Leadiant Biosciences Inc., Gaithersburg, MD 20878 10/2018.
2) Schwartz, Robert MD, Jyonouchi, Harumi MD et al. Pediatric Severe Combined Immunodeficiency October 11, 2018 Medscape.

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Date: February 14, 2019

