Effective Date 4/15/2024
Coverage Policy Number IP0572

Beremagene geperpavec-svdt

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Related Coverage Resources

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

This policy supports medical necessity review for beremagene geperpavec-svdt (**Vyjuvek™**).

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Beremagene geperpavec-svdt (Vyjuvek) is considered medically necessary when the following are met:

1. **Dystrophic Epidermolysis Bullosa.** Individual meets **ALL** of the following criteria:
   A. Age 6 months or older
   B. Documented diagnosis of dystrophic epidermolysis bullosa confirmed by genetic testing showing pathogenic, or likely pathogenic, variant in the collagen type VII alpha 1 chain (*COL7A1*) gene

   C. Documentation (chart notes, photographs) within the last 3 months of **ALL** of the following:
      i. At least **ONE** clinical feature of dystrophic epidermolysis bullosa

Examples of clinical features of dystrophic epidermolysis bullosa include but are not limited to blistering, skin erosion, and scarring.

ii. Identification of open wound(s) that will be receiving treatment (i.e., target wound[s])
iii. Target wound(s) is/are clean in appearance, has/have adequate granulation tissue and vascularization, and does/do not appear infected
iv. Squamous cell carcinoma has been ruled out for the target wound(s)

D. Prescriber attestation that individual is receiving concomitant standard of care wound prevention and/or treatment
E. Medication is prescribed by, or in consultation with, a dermatologist or wound care specialist

Dosing. ONE of the following dosing regimens:[1]
1. For those 6 months of age to less than 3 years of age, the dose is up to 0.8 mL (1.6×10^9 plaque forming units) topically once weekly
2. For those greater than 3 years of age, the dose is up to 1.6 mL (3.2×10^9 plaque forming units) topically once weekly

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When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

Continuation of beremagene geperpavec-svdt (Vyjuvek) is considered medically necessary for Dystrophic Epidermolysis Bullosa when the above medical necessity criteria are met AND there is documentation (in clinic/office notes) of beneficial response as evidenced by **BOTH** of the following:
1. Target wound(s) remain open
2. Target wound(s) has decreased in size from baseline

Authorization Duration

Initial approval duration: up to 6 months
Reauthorization approval duration: up to 6 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):
1. **Combination use with Filsuvez (birch triterpenes topical gel).** Combination use of Vyjuvek and Filsuvez have not been studied.[7]

Coding Information

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J3590	Unclassified biologic

Background

OVERVIEW
Vyjuvek, a herpes-simplex virus type-1 (HSV-1) vector-based gene therapy, is indicated for the treatment of wounds in patients ≥ 6 months of age with **dystrophic epidermolysis bullosa** (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene.[1]

Vyjuvek is a live, replication defective HSV-1-based vector that has been genetically modified to express the human type VII collagen (COL7) protein.[1] Mutation(s) in the COL7A1 gene result in reduced or absent levels of biologically active COL7 in patients with DEB. COL7 protein is a crucial component of anchoring fibrils that are essential for maintaining skin integrity. Application of Vyjuvek to wounds results in transcription of the encoded human COL7A1 and production and secretion of COL7 by the cell in its mature form. The COL7 molecules form anchoring fibrils that hold the epidermis and dermis together.

DEB usually presents at birth and is divided into two major types depending on the pattern of inheritance: recessive DEB (RDEB) and dominant DEB (DDEB).[6] All subtypes of DEB are caused by mutations in the gene coding COL7A1 leading to extreme skin fragility.[4,6] The hallmark of DEB is scarring of blisters, both on the skin and on other mucosal surfaces.[4]

Clinical Efficacy
GEM-3, a Phase III, double-blind, placebo-controlled, intrapatient randomized, pivotal study, assigned patients with DEB to treat two similarly sized wounds; one with Vyjuvek and one with placebo for 26 weeks (N = 31).[2] Eligible patients were ≥ 6 months of age presenting with a clinical diagnosis of DEB, characterized by blistering, wounds, and scarring and confirmed by genetic testing including COL7A1. The appearance of the wounds was to be clean with adequate granulation tissue, excellent vascularization, and to not appear infected. Patients receiving immunotherapy, chemotherapy, or other investigational products were not included. In addition, wound sites with current evidence or a history of squamous-cell carcinoma or active infection were excluded as sites for Vyjuvek (or placebo) application. Vyjuvek or placebo was applied only to open wounds. Wounds were evaluated weekly to determine continued application of Vyjuvek or placebo. If a healed wound reopened, application was resumed; if the wound remained closed, application was omitted. All but one patient had the recessive DEB genotype. At Month 6, significantly more Vyjuvek- vs. placebo-treated wounds were completely healed (67% vs. 22%, respectively; P = 0.002) [primary endpoint]. Similar results were observed at Month 3 favoring Vyjuvek vs. placebo for complete wound healing (71% vs. 20%, respectively; P < 0.001). Durability (complete wound healing at both Months 3 and 6) was seen in 50% vs. 7% of Vyjuvek- vs. placebo-treated wounds, respectively (difference 43%; 95% confidence interval: 23%, 63%). One patient had a chronic secondary wound of the back measuring > 100 cm^2 that had been open for > 10 years. Following Vyjuvek treatment, the patient was able to resume activities of daily living, including showering, which had not previously been possible due to the open nature of the wound.

Dosing Information
Only a healthcare professional should apply Vyjuvek either in a healthcare setting (e.g., clinic) or the home setting.[1] The recommended dose is based on age (see Table 1) and applied topically to wound(s) once weekly. It may not be possible to apply Vyjuvek to all the wounds at each treatment visit. Vyjuvek should be applied to wounds until they are closed before selecting new wound(s) to treat. Prioritize weekly treatment to previously treated wounds if they re-open. Individuals who are pregnant should not prepare or apply VYJUVEK gel and should avoid direct contact with the treated wounds or dressings from treated wounds. If a dose is missed, apply Vyjuvek as soon as possible and resume weekly dosing thereafter. Vyjuvek is applied to the selected wound(s) in droplets spaced evenly within the wound, approximately 1 cm x 1 cm apart. The resulting droplet pattern should loosely resemble a grid. Table 2 provides a reference dose based on wound size. A hydrophobic dressing is placed on top the Vyjuvek droplets, and a standard dressing is placed on top of the hydrophobic

dressing. The wound dressing should not be changed for approximately 24 hours after Vyjuvek gel administration.

Table 1. Maximum Weekly Dose by Age.[1]

Age Range	Maximum Weekly Dose	Maximum Weekly Volume*
≥ 6 months to < 3 years	1.6 x 10^9 PFUs	0.8 mL
≥ 3 years	3.2 x 10^9 PFUs	1.6 mL

* Maximum weekly volume after mixing Vyjuvek biological suspension with excipient gel; PFUs – Plaque forming units.

Table 2. Reference Dose by Wound Size.[1]

Area	Dose	Volume
< 20 cm^2	4 x 10^8 PFUs	0.2 mL
≥ 20 cm^2 to < 40 cm^2	8 x 10^8 PFUs	0.4 mL
≥ 40 cm^2 to ≤ 60 cm^2	1.2 x 10^9 PFUs	0.6 mL

PFUs – Plaque forming units.

Guidelines

Vyjuvek is not addressed in available guidelines. According to a position statement by the **European Reference Network for Rare Skin Diseases** (2021), wound care is the cornerstone of treatment for patients with DEB.[5] Careful and complete skin and wound assessment should be undertaken regularly, at least every 6 months. The healing rate of chronic wounds should be closely monitored, by checking wound edges.

The diagnosis of DEB is based on a combination of clinical features, family history, and laboratory findings.[5] Laboratory techniques include immunofluorescence mapping, transmission electron microscopy, and molecular genetic testing. Whenever possible, laboratory diagnosis should be performed in a specialized DEB center. Genetic testing is the gold standard for the diagnosis of DEB, since it provides a definitive diagnosis and classification of the major DEB type and in many cases the subtype.

An **international consensus best practice guideline** on skin and wound care in EB (2017) notes that EB is a lifelong disease that requires specialist intervention and consideration to minimize complications and improve quality of life.[6] Management should take place in a specialized center by a multi-disciplinary team, ideally. Definitive diagnosis is most commonly made from analysis of a skin biopsy using positive immunofluorescence, antigenic mapping, and transmission electron microscopy.[6] These key diagnostic tools help confirm diagnosis and indicate the particular subtype of EB. Due to the rarity of expertise and facilities, diagnosis is generally made using immunofluorescence and antigen mapping. Some laboratories are moving towards molecular diagnosis from exome sequencing of a panel of known skin fragility genes. Experienced clinicians can often make a provisional diagnosis on clinical observations, but a definitive diagnosis will always be required.

References

1. Vyjuvek™ biological suspension [prescribing information]. Pittsburgh, PA: Krystal Biotech; May 2023.
2. Guide SV, Gonzalez ME, Bagci IS, et al. Trial of beremagene geperavec (B-VEC) for dystrophic epidermolysis bullosa. *N Engl J Med.* 2022;387(24):2211-2219.
3. Payne AS. Topical gene therapy for epidermolysis bullosa. *N Engl J Med.* 2022;387(24):2281-2284.
4. Has C, Bauer JW, Bolling MC et al. Consensus and reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol.* 2020;183:614-627.
5. Has C, El Hachem M, Buckova H, et al. Practical management of epidermolysis bullosa: consensus clinical position statement from the European Reference Network for Rare Skin Diseases. *J Eur Acad Derm Venereol.* 2021;35:2349-2360.
6. Denyer J, Pillay E, Clapham J. Best practice guidelines for skin and wound care in epidermolysis bullosa. An International Consensus. *Wounds International.* 2017. Available at: https://af13d689-15eb-4199-8733-e91a7bb8ae3f.usrfiles.com/ugd/af13d6_01ed147ab87e49c584c20a917c47f19f.pdf. Accessed on: June 26, 2023

7. Kern JS, Sprecher E, Fernandez MF, et al. Efficacy and safety of Olegel-S10 (birch triterpenes) for epidermolysis bullosa: results from the phase III randomized double-blind phase of the EASE study. *Br J Dermatol*. 2023;188:12-21.