Vyjuvek (beremagene geperpavec-svdt)

Summary

Epidermolysis Bullosa (EB) is a group of inherited skin disorders characterized by exceedingly fragile skin that blisters, erodes, and scars in response to minimal friction or trauma. Four main types are EB simplex, dystrophic EB (DEB), junctional EB, and Kindler syndrome. The severity and presentation of symptoms, typically starting at birth or during infancy, differ significantly across types and subtypes. The US sees an estimated birth of 200 children per year with EB.

Dystrophic EB (DEB), caused by mutations in the COL7A1 gene that diminish or obstruct the production of type VII collagen (C7), is one such subtype. C7 is crucial for skin strength and stability, primarily constituting anchoring fibrils, structures attaching the epidermal basement membrane to the dermis. In the absence of functional C7, skin fragility intensifies and separates easily. DEB can be inherited as a dominant or recessive trait, with recessive types (RDEB) being the most severe due to mutations in both copies of the COL7A1 gene. Dominant DEB (DDEB) is milder, resulting from mutations in a single COL7A1 gene copy. It is estimated that fewer than 5000 individuals in the US live with DEB.

EB management is generally supportive, with wound care, protective bandaging, pain management, therapy, nutritional regulation, infection control, and carcinoma monitoring. Treatment usually takes

place at specialized EB centers. However, there is a pressing need for treatments to improve outcomes for EB patients, especially those with dystrophic types.

Vyjuvek (beremagene geperpavec-svdt or B-VEC), a product by Krystal Biotech Inc., is the first FDA-approved treatment for wounds linked with DEB. It was approved by the FDA on 05/19/2023 for the treatment of DEB in patients aged six months or older, with either recessive or dominant DEB. Vyjuvek holds the distinction of being the first approved product in the DEB space and the first approved topical redosable gene therapy. It delivers functional human COL7A1 genes directly to the skin of affected patients, expressing functional collagen VII to form anchoring fibrils and stabilize the fragile skin.

Definitions

"Anchoring fibrils" are structural components of the skin that connect the epidermal basement membrane to the dermis, thereby maintaining skin integrity.

"Beremagene geperpavec-svdt (Vyjuvek)" is a gene therapy medication used to treat DEB. Vyjuvek introduces a functional version of the COL7A1 gene into the patient's skin cells, aiming to enable the production of collagen VII.

"Collagen VII (C7)" is a protein that is integral to skin strength and stability. It forms the major part of anchoring fibrils, which attach the epidermal basement membrane to the dermis.

"COL7A1 gene" is the gene responsible for the production of collagen VII. Mutations in this gene cause dystrophic epidermolysis bullosa.

"Dominant DEB (DDEB)" is a less severe form of DEB, resulting from mutations in a single copy of the COL7A1 gene.

"Dystrophic Epidermolysis Bullosa (DEB)" is one of the four main types of EB. It occurs due to mutations in the COL7A1 gene, which cause a reduction or absence of collagen VII production.

"Epidermolysis Bullosa (EB)" is a group of rare, inherited skin conditions that cause skin to become incredibly fragile, resulting in blisters and tears even from minor friction or trauma.

"Gene therapy" is a type of treatment that involves introducing, altering, or suppressing a gene to treat a disease.

"Geneticist"is an expert in the field of genes, hereditable diseases, and the managment and treatment of hereditable diseases.

"Genetic testing" is a general term for medical procedures aimed at analyzing a person's DNA for mutations or alterations in one's genes. Genetic tests may include, but are not limited to, targeted gene

sequencing (testing for only specific genes or regions of the genome), multigene panel testing (testing multiple genes or multiple regions of the genome simultaneously), or exome sequencing (or "whole exome sequencing" assessing for gene alterations or mutations amongst only protein-coding DNA/genome).

"Immunofluorescence Mapping (IFM)" is a diagnostic technique used to visualize the presence and location of proteins in skin tissue. In the context of DEB, it can identify alterations or absence of type VII collagen along the basement membrane zone (BMZ).

"Pathogenic variant": This term refers to changes in the DNA sequence of a gene that has been confirmed to increase the risk of disease. In the context of DEB, pathogenic variants in the COL7A1 gene result in dysfunctional collagen VII production.

"Recessive DEB (RDEB)" is a more severe form of DEB, caused by mutations in both copies of the COL7A1 gene.

"Squamous cell carcinoma" is a type of skin cancer that can develop in severe cases of RDEB.

"Transmission Electron Microscopy (TEM)" is a microscopy technique that provides detailed, high-resolution images of cellular structures. It can be used to observe the structure of anchoring fibrils and detect subepidermal blistering in DEB patients.

Medical Necessity Criteria for Initial Authorization

The Plan considers Vyjuvek (beremagene geperpavec-svdt) medically necessary when ALL of the following criteria are met:

1. The medication is prescribed by or in consultation with a geneticist, dermatologist, or pathologist who is experienced in the diagnosis and treatment of epidermolysis bullosa (EB); *AND*
2. The member is 6 months of age or older; *AND*
3. The member has a clinical diagnosis of dystrophic epidermolysis bullosa (DEB) confirmed by at least ONE of the following methods:
    a. Genetic testing techniques, such as targeted gene sequencing, multigene panel testing, exome sequencing, or other genomic methods that identify EITHER:
        i. recessive DEB (RDEB), confirmed by two copies of pathogenic variants (biallelic) in the collagen type VII alpha 1 chain (COL7A1) gene. The type of mutations (e.g., nonsense, missense, splice-site mutations, or small insertions/deletions) should be specified; *or*
        ii. dominant DEB (DDEB), confirmed by a single copy of a pathogenic variant (heterozygous) in the COL7A1 gene. The specific type of mutation should be defined; *or*

b. Immunofluorescence Mapping (IFM) indicating altered or missing type VII collagen along the basement membrane zone (BMZ); *or*
c. Transmission Electron Microscopy (TEM) displaying either underdeveloped or rudimentary anchoring fibrils or subepidermal blistering; *AND*

4. Documentation of ALL of the following:
    a. Measurements of wound size at baseline; *and*
    b. A comprehensive treatment plan inclusive of wound care, pain management, nutritional support, and physical therapy as required; *and*
    c. Vyjuvek (beremagene geperpavec-svdt) will be administered by a healthcare professional, either in a professional healthcare setting (e.g., clinic) or the home setting; *AND*
5. The prescribed dosage meets ONE of the following:
    a. For members aged 6 months to <3 years, up to 0.8 mL per week (i.e., a maximum weekly dose of 1.6×10^9 plaque forming units [PFU]); *or*
    b. For members aged 3 years and older, up to 1.6 mL per week (i.e., a maximum weekly dose of 3.2×10^9 PFU).

    NOTE: Vyjuvek (beremagene geperpavec-svdt) must be used within the aforementioned limits unless a higher quantity has been approved based on a review of a medication exception request. The prescribing provider must offer a clinical rationale for any request exceeding these dosage limits.

If the above prior authorization criteria are met, the requested medication will be approved for an initial approval duration of 12 weeks (3 months).

Medical Necessity Criteria for Reauthorization

Reauthorization for 6 months will be granted if the member has recent (within the last 3 months) clinical chart documentation demonstrating ALL of the following criteria:

1. The requested medication is prescribed by or in consultation with a geneticist, dermatologist, or pathologist; *AND*
2. The member has experienced a documented improvement in wound healing while on Vyjuvek (beremagene geperpavec-svdt). This improvement must be validated by clinical documentation showing a reduction in wound size, with measurements taken at baseline and at each follow-up visit, demonstrating consistent progress in healing; *AND*
3. The member has demonstrated adherence to the Vyjuvek treatment protocol, with applications conducted regularly according to instructions, i.e., applied by a healthcare professional once a week; *AND*
4. There is no recorded evidence of unacceptable toxicity or adverse reactions to Vyjuvek (beremagene geperpavec-svdt) that would necessitate discontinuation of treatment. Routine

monitoring for common adverse events such as pruritus, chills, and skin squamous-cell carcinoma (SCC) should be reflected in the clinical chart; *AND*

5. There is no clinical evidence indicating disease progression, as defined by a significant exacerbation of existing wounds that have been treated. This should be confirmed by clinical evaluations and documented in the member's medical record.

Experimental or Investigational / Not Medically Necessary

Vyjuvek (beremagene geperpavec-svdt) for any other indication or use is considered not medically necessary by the Plan, as it is deemed to be experimental, investigational, or unproven. Non-covered indications include, but are not limited to, treatment of other skin disorders caused by genetic mutations.

Applicable Billing Codes (HCPCS/CPT Codes)

Service(s) name	
CPT/HCPCS Codes considered medically necessary if criteria are met:	
Code	*Description*
99202	Office or other outpatient visit for the evaluation and management of a new patient, which requires a medically appropriate history and/or examination and straightforward medical decision making. When using total time on the date of the encounter for code selection, 15 minutes must be met or exceeded.
99203	Office or other outpatient visit for the evaluation and management of a new patient, which requires a medically appropriate history and/or examination and low level of medical decision making. When using total time on the date of the encounter for code selection, 30 minutes must be met or exceeded.
99204	Office or other outpatient visit for the evaluation and management of a new patient, which requires a medically appropriate history and/or examination and moderate level of medical decision making. When using total time on the date of the encounter for code selection, 45 minutes must be met or exceeded.
99205	Office or other outpatient visit for the evaluation and management of a new patient, which requires a medically appropriate history and/or examination and high level of medical decision making. When using total time on the date of the encounter for code selection, 60 minutes must be met or exceeded.
99211	Office or other outpatient visit for the evaluation and management of an established patient that may not require the presence of a physician or other qualified health care professional

99212	Office or other outpatient visit for the evaluation and management of an established patient, which requires a medically appropriate history and/or examination and straightforward medical decision making. When using total time on the date of the encounter for code selection, 10 minutes must be met or exceeded.
99213	Office or other outpatient visit for the evaluation and management of an established patient, which requires a medically appropriate history and/or examination and low level of medical decision making. When using total time on the date of the encounter for code selection, 20 minutes must be met or exceeded.
99214	Office or other outpatient visit for the evaluation and management of an established patient, which requires a medically appropriate history and/or examination and moderate level of medical decision making. When using total time on the date of the encounter for code selection, 30 minutes must be met or exceeded.
99215	Office or other outpatient visit for the evaluation and management of an established patient, which requires a medically appropriate history and/or examination and high level of medical decision making. When using total time on the date of the encounter for code selection, 40 minutes must be met or exceeded.
J3401	Beremagene geperpavec-svdt for topical administration, containing nominal 5 x 109 PFU/ml vector genomes, per 0.1 ml
ICD-10 codes considered medically necessary if criteria are met:	
Code	*Description*
Q81.2	Epidermolysis bullosa dystrophica
Z48.00	Encounter for change or removal of nonsurgical wound dressing
Z48.01	Encounter for change or removal of surgical wound dressing
Z48.02	Encounter for removal of sutures

Appendix

Clinical Studies

The efficacy and safety of Vyjuvek were assessed in two key clinical trials, Phase III GEM-3 and Phase I/II GEM-1, studying the effectiveness of beremagene geperpavec-svdt (B-VEC) in the treatment of dystrophic epidermolysis bullosa (DEB).

In the Phase III GEM-3 trial, the double-blind randomized placebo-controlled study included 31 participants, predominantly aged 18 years or younger, suffering from DEB. Each participant had two wounds treated weekly – one with B-VEC, and one with placebo, for a period of 26 weeks. The primary

endpoint was complete wound healing at 6 months. Results indicated significantly higher wound healing in wounds treated with B-VEC) compared to those treated with placebo (67% vs. 22%, 95% CI [24-68] p=0.002, number needed to treat [NNT]=3). The secondary end point, complete healing at 3 months, was significantly higher in those exposed to B-VEC versus placebo (71% vs. 20%, 95% CI [29-73], p<0.001, NNT=2). A total of 18 patients experienced at least 1 adverse event, most of which were mild or moderate.

The Phase I/II GEM-1 trial was a single-center open-label trial with intra-patient comparison, conducted over 12 weeks. Nine patients with RDEB were enrolled, with three enrolling twice for treatment of a new set of target wounds. The primary outcome was wound closure, defined as a reduction in wound surface area of ≥ 95% from baseline by study week 12. Results revealed that all but one target wound treated with B-VEC achieved closure after 3 months. B-VEC was found to be significantly superior to placebo for wound closure, and the time to and duration of wound closure numerically favored B-VEC over placebo.

References

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Clinical Guideline Revision / History Information

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