UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Dermatology – Gene Therapy – Vyjuvek Utilization Management Medical Policy
- Vyjuvek™ (beremagene geperpavec-svdt topical gel – Krystal Biotech)

REVIEW DATE: 06/18/2025; selected revision 06/25/2025

OVERVIEW

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

Disease Overview

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 variants 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. 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 epidermolysis bullosa (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. 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.

POLICY STATEMENT

Prior Authorization is recommended for medical benefit coverage of Vyjuvek. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indication. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days. Because of the specialized skills required for evaluation and diagnosis of patients treated with Vyjuvek as well as the monitoring required for adverse events and long-term efficacy, approval requires Vyjuvek to be prescribed by or in consultation with a physician who specializes in the condition being treated.

Documentation: Documentation is required for use of Vyjuvek as noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, prescription claims records, prescription receipts, and/or other information.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Vyjuvek is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Dystrophic Epidermolysis Bullosa.** Approve for the duration outlined below if the patient meets ONE of the following (A or B):
   Note: For new wound(s) the patient is directed to Initial Therapy criteria. If the patient is continuing to treat the same wound(s) the patient is directed to criteria for Patient Currently Receiving Vyjuvek on Previously Treated Wound(s).
   - **A)** Initial Therapy: Approve for 6 months if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient is ≥ 6 months of age; AND
     - **ii.** The diagnosis is confirmed by genetic testing showing a pathogenic variant in the collagen type VII alpha 1 chain (*COL7A1*) gene **[documentation required]**; AND
     - **iii.** Patient meets ALL of the following (a, b, and c):
       - **a)** Patient has at least one clinical feature of dystrophic epidermolysis bullosa **[documentation required]**; AND
         Note: Examples of clinical features of dystrophic epidermolysis bullosa include but are not limited to blistering, wounds, and scarring.
       - **b)** Patient has one or more open wound(s) that will be treated (i.e., "target wound[s]); AND
       - **c)** Target wound(s) meets ALL of the following, according to the prescriber [(1), (2), and (3)]:
         - **(1)** Target wound(s) is clean in appearance and does not appear to be infected; AND
         - **(2)** Target wound(s) has adequate granulation tissue and vascularization; AND
         - **(3)** Squamous cell carcinoma has been considered for the target wound(s); AND
     - **iv.** The medication is prescribed by or in consultation with a dermatologist or wound care specialist; OR

Patient is Currently Receiving Vyjuvek on **Previously Treated Wound(s)**: Approve for 6 months if the patient meets ALL of the following (i, ii, and iii):

Note: If the patient is treating a new wound(s) not previously treated with Vyjuvek or a reopened recurrent wound(s), then refer to Initial Therapy criteria above.

v. According to the prescriber, the target wound(s) remains open; AND
vi. According to the prescriber, the target wound(s) has decreased in size from baseline; AND
vii. The medication is prescribed by or in consultation with a dermatologist or wound care specialist.

Dosing. Approve one of the following dosing regimens (A or B):

A) Patient is ≥ 6 months to < 3 years of age: Approve up to 0.8 mL (1.6×10^9 plaque forming units) topically once weekly.
Note: This is the maximum weekly volume after mixing Vyjuvek biological suspension with excipient gel.

B) Patient is ≥ 3 years of age: Approve up to 1.6 mL (3.2×10^9 plaque forming units) topically once weekly.
Note: This is the maximum weekly volume after mixing Vyjuvek biological suspension with excipient gel.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Vyjuvek is not recommended in the following situations:

1. **Combination use with Filsuvez (birch triterpenes topical gel).** Combination use of Vyjuvek and Filsuvez has not been studied.[7]

2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Vyjuvek™ topical gel [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 12, 2025.
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.

HISTORY

Type of Revision	Summary of Changes	Review Date
New Policy	--	06/28/2023
Selected Revision	**Dystrophic Epidermolysis Bullosa.** Criteria were divided into "Initial Therapy" and "Patient is Currently Receiving Vyjuvek". The approval duration for initial and continuation therapy are 3 months, previously criteria approved all patients for 6 months. Initial Therapy A documentation requirement was added to criteria for the confirmation of the diagnosis by genetic testing showing a pathogenic mutation in the collagen type VII alpha 1 chain (COL7A1) gene. A documentation requirement was added to criteria for one clinical feature of dystrophic epidermolysis bullosa. Criteria for one or more open wound(s) were clarified to address such wound(s) would be treated (referred to as "target wound[s]") and that, according to the prescriber, the target wound(s) meets all of the following criteria: is clean in appearance and does not appear to be infected, has adequate granulation tissue and vascularization, and squamous cell carcinoma has been ruled out. Patient is Currently Receiving Vyjuvek on Previously Treated Wound(s) Patients currently receiving Vyjuvek on previously treated wounds are required to have a target wound(s) that remains open, according to the prescriber and has decreased in size from baseline as demonstrated by wound measurements or photographs, according to the prescriber. The medication must also be prescribed by or in consultation with a dermatologist or wound care specialist with expertise in the management of dystrophic epidermolysis bullosa. Of note, if the patient is treating a new wound(s) not previously treated with Vyjuvek or reopened recurrent wound(s) the patient is directed to Initial Therapy criteria.	09/13/2023
Selected Revision	**Dystrophic Epidermolysis Bullosa.** Initial Therapy: The approval duration was changed to 6 months. Patient is Currently Receiving Vyjuvek on Previously Treated Wound(s): The approval duration was changed to 6 months.	09/27/2023
Selected Revision	**Dystrophic Epidermolysis Bullosa.** Patient is Currently Receiving Vyjuvek on Previously Treated Wound(s): The criterion requiring that the target wound(s) has decreased in size from baseline as demonstrated by wound measurements or photographs, according to the prescriber was modified to remove the requirement of wound measurements or photographs. The criterion now requires that according to the prescriber, the target wound(s) has decreased in size from baseline.	10/11/2023
Selected Revision	**Dystrophic Epidermolysis Bullosa:** Initial Therapy and Patient is Currently Receiving Vyjuvek on Previously Treated Wound(s). The criterion requiring that the medication is prescribed by or in consultation with a dermatologist or wound care specialist with expertise in the management of dystrophic epidermolysis bullosa was modified to remove the requirement of expertise in the management of dystrophic epidermolysis bullosa. The requirement now reads that the medication is prescribed by or in consultation with a dermatologist or wound care specialist. **Combination use with Filsuvez (birch triterpenes topical gel).** This condition was added to the Conditions Not Recommended for Approval.	01/24/2024
Annual Revision	No criteria changes.	06/26/2024
Annual Revision	**Dystrophic Epidermolysis Bullosa:** For diagnosis confirmed by genetic testing, rephrased the term "mutation" to "pathogenic variant" and "both alleles" was added to the criterion. The criterion was modified to Squamous cell carcinoma has been considered for the target wound(s)." Previously it stated "Squamous cell carcinoma has been ruled out for the target wound(s)."	06/18/2025
Selected Revision	**Dystrophic Epidermolysis Bullosa:** For diagnosis confirmed by genetic testing, the phrase "both alleles" was removed from the criterion.	06/25/2025