Vyjuvek™ (Beramagene Geperpavec-Svdt)

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Coverage Rationale

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Vyjuvek is proven and medically necessary for the treatment of wounds in patients with dystrophic epidermolysis bullosa (DEB) who meet all of the following criteria:

- For **initial therapy**, **all** of the following:
  - Patient is aged at least 6 months and older; **and**
  - Diagnosis of dystrophic epidermolysis bullosa (DEB); **and**
  - Submission of medical records (e.g., chart notes, laboratory values) confirming a mutation in the *collagen* type VII alpha 1 chain (COL7A1) gene; **and**
  - Patient has at least one recurrent or chronic open wound that meets **all** of the following criteria:
    - Adequate granulation tissue
    - Excellent vascularization
    - No evidence of active wound infection
    - No evidence or history of squamous cell carcinoma
  - Vyjuvek is prescribed by, or in consultation with, a dermatologist with expertise in the treatment of DEB; **and**
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**
  - Initial authorization will be issued for no more than 6 months and no more than 26 doses
- For **continuation of therapy**, **all** of the following:
  - Patient has previously been treated with Vyjuvek therapy
  - Patient had a positive clinical response to Vyjuvek therapy (e.g., decrease in wound size, increase in granulation tissue, complete wound closure); **and**
  - Wound(s) being treated to meet all of the following criteria:
    - Adequate granulation tissue
    - Excellent vascularization
    - No evidence of active wound infection
    - No evidence or history of squamous cell carcinoma
  - Vyjuvek is prescribed by, or in consultation with, a dermatologist with expertise in the treatment of DEB; **and**
  - Dosing is in accordance with the United States Food and Drug Administration approved labeling; **and**

- Reauthorization will be issued for no more than 6 months and no more than 26 doses

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS Code	Description
J3401	Beremagene geperpavec-svdt for topical administration, containing nominal 5 x 10⁹ PFU/ml vector genomes, per 0.1 ml

Diagnosis Code	Description
Q81.2	Epidermolysis bullosa dystrophica

Background

Dystrophic epidermolysis bullosa (DEB) is an ultra-rare genetic connective tissue disorder caused by mutations in the collagen type VII alpha 1 chain (COL7A1) gene.[1-2] The COL7A1 gene codes for type VII collagen (C7), a major component of structures in the skin called anchoring fibrils found in the epidermal basement membrane located between the epidermis (top layer of skin) and dermis (underlying layer). Mutations in the COL7A1 gene disrupt adhesion of the epidermis to the dermis. Patients with EB completely lack or are deficient in COL7A1, resulting in skin fragility and multiple recurring wounds that are difficult to manage. Over time, repeated blistering and fibrosis can lead to squamous-cell carcinoma, life-threating infections, and limb deformities. DEB may be inherited as a dominant or recessive trait; generally, RDEB is more severe than dominant disease (DDEB); however, there is considerable phenotypic overlap between types. DEB affects approximately 9,000 people globally, including approximately 3,000 people in the U.S. and approximately 3,000 in Europe. The current standard of care is supportive treatment with wound care and prevention of infection.

Vyjuvek is a topical gene therapy that uses a herpes simplex virus (HSV-1) to introduce a normal copy of the COL7A1 gene to patients' skin cells. Once Vyjuvek enters the nucleus of transduced cells, the vector genome is deposited episomally and as a result, COL7A1 transcripts are generated, allowing the cell to produce and secrete functional CO7A1 protein necessary for the formation of anchoring fibrils that bind the dermis and epidermis together, and blistered skin to be replaced with healthy skin. The COL7A1 gene does not incorporate itself into patients' chromosomes; therefore, patients must be treated with Vyjuvek repeatedly in order to continue producing healthy skin.

Benefit Considerations

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the member specific benefit plan document or in the medical or drug policy. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. Refer to the Policy and Procedure addressing the treatment of serious rare diseases.

Clinical Evidence

Proven

The efficacy of Vyjuvek gel in subjects one year of age and older with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the COL7A1 gene was evaluated in one randomized, double-blind, intra-subject placebo-controlled trial.[1-2] All study subjects

had clinical manifestations consistent with DEB and genetically confirmed mutation(s) in the COL7A1 gene. Two comparable wounds in each subject were selected and randomized to receive either topical application of Vyjuvek gel or the placebo (excipient gel) weekly for 26 weeks. The study enrolled 31 subjects (20 males and 11 females), including 30 subjects with autosomal recessive DEB and one subject with autosomal dominant DEB. The size of the Vyjuvek gel-treated wounds ranged from 2 to 57 cm^2 , with 74% of wounds < 20 cm2 and 19% from 20 to < 40 cm^2 . The size of the placebo gel-treated wounds ranged from 2 to 52 cm^2, with 71% of wounds < 20 cm^2 and 26% from 20 to < 40 cm^2 . The mean age of the subjects was 17 years (1 year to 44 years), including 61% pediatric subjects (n = 19, age from 1 year to < 17 years). Sixty-four percent of subjects were White; 19% were Asian, and the remainder were American Indian or Alaska Native. Efficacy was established on the basis of improved wound healing defined as the difference in the proportion of complete (100%) wound closure at 24 Weeks confirmed at two consecutive study visits 2 weeks apart, assessed at Weeks 22 and 24 or at Weeks 24 and 26, between the Vyjuvek gel-treated and the placebo gel-treated wounds. Efficacy was supported by the difference in the proportion of complete wound closure assessed at Weeks 8 and 10 or at Weeks 10 and 12 between the Vyjuvek gel-treated and the placebo gel-treated wounds. Complete (100%) wound closure was defined as durable wound closure evaluated at two consecutive visits two weeks apart. At 6 months, complete wound healing occurred in 67% of the wounds exposed to B-VEC as compared with 22% of those exposed to placebo (difference, 46 percentage points; 95% confidence interval [CI], 24 to 68; p = 0.002). Complete wound healing at 3 months occurred in 71% of the wounds exposed to B-VEC as compared with 20% of those exposed to placebo (difference, 51 percentage points; 95% CI, 29 to 73; p < 0.001). The mean change from baseline to week 22 in pain severity during wound-dressing changes was -0.88 with B-VEC and -0.71 with placebo (adjusted least-squares mean difference, -0.61; 95% CI, -1.10 to -0.13); similar mean changes were observed at weeks 24 and 26.

A total of 18 patients (58%) had at least one adverse event (Table 4). The majority of adverse events were mild or moderate in severity, as assessed by the investigators. Five serious adverse events occurred in 3 patients: 1 patient was hospitalized three times, once for diarrhea and twice for severe anemia; 1 patient was hospitalized for treatment of cellulitis; and 1 patient was hospitalized for a positive blood culture related to a hemodialysis catheter. None of the serious adverse events were considered to be related to B-VEC or placebo by the investigators. One adverse event, mild erythema, was considered to be related to B-VEC. No adverse events led to discontinuation of B-VEC or placebo. The most common adverse events were pruritus, chills, and squamous-cell carcinoma of the skin, each of which occurred in 3 patients (10%). All three cases of squamous-cell carcinoma occurred at wound sites that had not been exposed to B-VEC or placebo.

To determine potential immunogenicity, levels of antibodies against HSV-1 and C7 before and after treatment were assessed. Because of the difficulty of venipuncture in these patients, 22 of 31 patients (71%) had baseline serum samples. Among the patients with baseline samples, 14 of 22 patients (64%) had antibodies against HSV-1, a finding consistent with the prevalence of seropositivity in the U.S. population,21 and 1 of 22 patients (5%) had antibodies against C7. Among the patients with baseline samples, 19 had samples at both baseline and week 26, including the patient who had antibodies against C7. By week 26, seroconversion had occurred in 6 of 8 patients (75%) with no antibodies against HSV-1 at baseline (Fig. S4) and in 13 of 18 (72%) with no antibodies against C7 at baseline. No clinically significant immunologic reactions were reported. Treatment response to B-VEC was not associated with baseline HSV-1 serostatus (Table S5) or C7 seroconversion (Table S6).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

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

References

1. Vyjuvek [package insert]. Pittsburg, PA: Krystal Biotech, Inc.; May 2023.
2. Guide SV, Gonzalez ME, Bağcı IS, Agostini B, Chen H, Feeney G, Steimer M, Kapadia B, Sridhar K, Quesada Sanchez L, Gonzalez F, Van Ligten M, Parry TJ, Chitra S, Kammerman LA, Krishnan S, Marinkovich MP. Trial of Beremagene Geperpavec (B-VEC) for Dystrophic Epidermolysis Bullosa. N Engl J Med. 2022 Dec 15;387(24):2211-2219. doi: 10.1056/NEJMoa2206663. PMID: 36516090.

3. A Phase III Efficacy and Safety Study of Beremagene Geperpavec (**B-VEC**, Previously "KB103") for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). ClinicalTrials.gov identifier: NCT04491604. Updated February 17, 2023. Accessed June 30, 2023. https://classic.clinicaltrials.gov/ct2/show/study/NCT04491604.
4. Open Label Treatment of Beremagene Geperpavec (B-VEC). ClinicalTrials.gov identifier: NCT04917874. Updated April 2023. Accessed June 30, 2023. https://classic.clinicaltrials.gov/ct2/show/NCT04917874.

Policy History/Revision Information

Date	Summary of Changes
01/01/2024	**Applicable Codes** • Updated list of applicable HCPCS codes to reflect annual edits; replaced C9399, J3490, and J3590 with J3401 **Supporting Information** • Archived previous policy version 2023D00127B

Instructions for Use

This Medical Benefit Drug Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Benefit Drug Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Benefit Drug Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Benefit Drug Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.