Policy Number	**RX501.164**
Policy Effective Date	**5/7/2026**

Gene Therapies for Treatment of Wounds in Dystrophic Epidermolysis Bullosa

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of care developed by: nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated, and coverage is not required for non-formulary drugs.

Coverage

Beremagene geperpavec-svdt (Vyjuvek®)
Beremagene geperpavec-svdt (Vyjuvek) **may be considered medically necessary** for adult and pediatric individuals if they meet criteria 1 through 2:

1. Diagnosis of dystrophic epidermolysis bullosa confirmed by:
   a. Documented mutation(s) in the *COL7A1* gene.
   b. Presence of clinical manifestations of dystrophic epidermolysis bullosa including, but not limited to, chronic and recurring wounds of the skin, blistering of skin, and blistering, ulcerations, and scarring of visceral mucosal tissues.
2. No active infection, active squamous cell carcinoma, or history of squamous cell carcinoma in the targeted wound(s).

Beremagene geperpavec-svdt (Vyjuvek) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Prademagene zamikeracel (Zevaskyn™)
Prademagene zamikeracel (Zevaskyn) **may be considered medically necessary** for the treatment of wounds in adult and pediatric individuals diagnosed with recessive dystrophic epidermolysis bullosa (RDEB) conditions when the following criteria are met.

1. The individual must have wounds associated with recessive dystrophic epidermolysis bullosa (RDEB);

2. **AND ALL** the following:
   a. Documented biallelic pathogenic mutations in the collagen type VII alpha 1 chain (*COL7A1*) gene;
   b. Positive expression of the non-collagenous region 1 of the type 7 collagen protein (NC1+) in the skin;
   c. Presence of at least one chronic wound (e.g., stage 2 wounds that have an area ≥ 20 cm^2) and have been present for at least 3 months;
   d. Presence of clinical manifestations of RDEB, such as extensive skin blistering, skin erosions, or scarring.

Prademagene zamikeracel (Zevaskyn) **is considered experimental, investigational and/or unproven** for all other non-Food and Drug Administration approved indications.

Policy Guidelines

Beremagene geperpavec-svdt

Recommended Dose

Per the FDA-Label, beremagene geperpavec-svdt should be applied once weekly by a healthcare professional. It may not be possible to apply beremagene geperpavec-svdt to all the wounds at each treatment visit. Beremagene geperpavec-svdt should be applied to wounds until they are closed before selecting new wounds, and previously treated wounds that re-open should be prioritized over new wounds.

PG1. Dosing Recommendations

Age Range	Maximum Weekly Dose (plaque forming units)	Maximum Weekly Volume (mL)*
< 3 years old	2×10^9	1
≥ 3 years old	4×10^9	2

* Maximum weekly volume is the volume after mixing beremagene geperpavec-svdt biological suspension with excipient gel.

Prademagene zamikeracel

Recommended Dose

Per the FDA-label, prademagene zamikeracel is for autologous topical application on wounds only.

- The recommended dose of prademagene zamikeracel is based on the surface area of the wound(s).
- One sheet of prademagene zamikeracel covers an area of 41.25 cm^2.
- Up to twelve prademagene zamikeracel sheets may be manufactured from the patient biopsies and supplied for potential use.

Description

Dystrophic Epidermolysis Bullosa

Dystrophic epidermolysis bullosa is a rare and clinically and genetically heterogeneous skin fragility disorder characterized by blistering of the skin and mucosal membranes that heal with scarring. The onset of symptoms is usually at birth or in early childhood. There may be associated complications, including malnutrition, anemia, infection, and skin cancer. Death may occur prematurely due to multiple causes, including infection, progression of disease, organ failure, and malignancy. (3)

Dystrophic epidermolysis bullosa is caused by variant in the *COL7A1* gene, encoding the alpha-1 chain of type VII collagen. Collagen VII is the main structural constituent of the anchoring fibrils located below the lamina densa of the epidermal basement membrane zone, which hold the epidermis and dermis together and is essential for maintaining the integrity of the skin. It can be inherited in an autosomal dominant or recessive fashion. (4-6) Recessive dystrophic epidermolysis bullosa is more severe than dominant disease variants; however, there is a considerable phenotypic overlap among all types. More than 600 distinct mutations in the *COL7A1* gene have been identified in dystrophic epidermolysis bullosa. Although a few mutations are recurrent in some populations due to the founder effect, most families carry unique mutations. (7)

The 2020 consensus classification (3) recognizes four major subtypes and several rare, dominant or recessive subtypes of dystrophic epidermolysis bullosa.

1. Localized dominant dystrophic epidermolysis bullosa
2. Intermediate dominant dystrophic epidermolysis bullosa (previously known as generalized dominant dystrophic epidermolysis bullosa)
3. Intermediate recessive dystrophic epidermolysis bullosa (previously known as recessive dystrophic epidermolysis bullosa generalized intermediate, non-Hallopeau-Siemens recessive dystrophic epidermolysis bullosa)
4. Severe recessive dystrophic epidermolysis bullosa (previously recessive dystrophic epidermolysis bullosa generalized severe, Hallopeau-Siemens recessive dystrophic epidermolysis bullosa)

Based on the National Epidermolysis Bullosa Registry in the U.S., the incidence of epidermolysis bullosa was 19.57 per million live births and prevalence of 11.07 per million population over the period from 1986 to 2002. The numbers for recessive dystrophic epidermolysis bullosa was 3.05 per million live births and 1.35 per million population, respectively. (8)

Prior to the Food and Drug Administration approval of gene therapies for dystrophic epidermolysis bullosa, there were no FDA-approved treatments for dystrophic epidermolysis bullosa. Disease management was supportive including wound care, pain

management, control of infection, nutritional support, and prevention and treatment of complications. FDA previously approved a Humanitarian Devices Exemption for the product, Composite Cultured Skin to be used as a wound dressing in patients with mitten hand deformity due to recessive dystrophic epidermolysis bullosa as an adjunct to standard autograft procedures [i.e., skin grafts and flaps for covering wounds and donor sites created after the surgical release of hand contractions (i.e., "mitten" hand deformities)].

Regulatory Status
In May 2023, beremagene geperpavec-svdt (Vyjuvek; Krystal Biotech) was approved by the FDA 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.

In September 2025, the FDA approved a label update for Vyjuvek that expands the Vyjuvek eligible patient population to include dystrophic epidermolysis bullosa (DEB) patients from birth. (10)

In April 2025, prademagene zamikeracel (Zevaskyn; Abeona Therapeutics) was approved by the U.S. FDA for the treatment of wounds in adult and pediatric patients with recessive dystrophic epidermolysis bullosa.

Rationale

This policy is based on the U.S. Food and Drug Administration labeled indications for beremagene geperpavec-svdt (Vyjuvek) and prademagene zamikeracel (Zevaskyn™) and a review of relevant professional guidelines and position statements.

Beremagene geperpavec-svdt (Vyjuvek) (1)
The efficacy of Vyjuvek gel was evaluated in one randomized, double-blind, intra-patient placebo-controlled study (NCT04491604). The study enrolled patients with dystrophic epidermolysis bullosa (DEB) with genetically confirmed mutation(s) in the *COL7A1* gene and who had two cutaneous wounds with similar size, appearance, and anatomical location. Two comparable wounds in each patient were selected and randomized to receive either topical application of Vyjuvek gel or the placebo (excipient gel) weekly for 26 weeks.

A total of 31 patients were treated with Vyjuvek and placebo. The demographic characteristics of the population were as follows: the mean age was 17 years (range 1 to 44 years) including 19 pediatric patients (aged 1 to 16 years), 20 patients (65%) were male, 20 patients (65%) were White, 6 patients (19%) were Asian, and 5 patients (16%) were American Indian or Alaskan Native. Thirty patients had autosomal recessive DEB, and one patient had autosomal dominant DEB. The size of the Vyjuvek gel-treated wounds ranged from 2 to 57 cm^2, with 74% of wounds < 20 cm^2 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.

Primary efficacy outcome measure was 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. Other efficacy outcome measures were 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. The efficacy results are summarized in Table 1.

Table 1. Summary of the Efficacy Results for Vyjuvek Gel

Wound Closure Assessment Timepoints	**Complete Wound Closure, n(%) Vyjuvek gel (N=31)**	**Complete Wound Closure, n(%) Placebo gel (N=31)**	**Treatment Difference (95% CI)**	**p-value**
Weeks 22 & 24 or Weeks 24 & 26	20 (65)	8 (26)	39% (14, 63)	0.012
Weeks 8 & 10 or Weeks 10 & 12	21 (68)	7 (23)	45% (22, 69)	0.003

CI: confidence interval.

Prademagene zamikeracel (Zevaskyn™) (2)

The efficacy of Zevaskyn was evaluated in a multi-center, randomized, intrapatient-controlled study (VIITAL; NCT04227106). The study compared the application of Zevaskyn to the standard of care treatment in patients with wounds associated with recessive dystrophic epidermolysis bullosa (RDEB). For enrollment, the patients were required to have at least one pair of matched, large (at least one wound ≥20 cm^2 for treatment and at least one wound ≥20 cm^2 for control) and chronic wounds (open for ≥6 months) associated with RDEB. Patients with current or history of squamous cell carcinoma (SCC) at the treatment site were excluded. Matched wound pairs were randomized in a 1:1 ratio to receive either Zevaskyn (up to 6 sheets) or control treatment (standard of care wound dressings).

A total of 86 wounds in 11 patients were enrolled and treated with Zevaskyn or standard of care in the study. The demographic characteristics of the population were as follows: the mean age was 23 years (range 6 to 40 years) including 2 pediatric patients (aged 6 and 16 years), 7 patients (64%) were female, 10 patients (91%) were White, 1 patient (9%) was of

unknown race, and 2 patients (18%) were Hispanic or Latino. The wounds assessed in the study at baseline had been open for a median of 5 years (range 0.5-21 years).

The co-primary efficacy outcome measures were 1) proportion of randomized wound pairs with at least 50% healing at Month 6 with confirmation of wound healing two weeks later as assessed using baseline digital photography by the Investigator, and 2) pain reduction as assessed by the mean differences in patient-reported pain scores using the Wong-Baker FACES scale between randomized wound pairs at Month 6. Secondary outcome measures were proportion of randomized wound pairs with complete wound healing defined as reepithelialization with no drainage or erosion and presence of only minor crusting from baseline at Month 3 and at Month 6 with confirmation of wound healing two weeks later. The efficacy results are summarized in Table 2.

Table 2. Efficacy Results for VIITAL Study (N=86 wounds)

Efficacy Endpoint	**Zevaskyn (N=43 wounds)**	**Control (N=43 wounds)**	**P value**
Proportion of randomized wound pairs healed ≥50% from baseline at Month 6[a] n (%)	35 (81%)	7 (16%)	<0.0001
Mean pain reduction from baseline at Month 6[b] Mean (SD)	-3.07 (3.19)	-0.90 (2.73)	0.0002
Proportion of randomized wound pairs completely healed from baseline at Month 3 n (%)	6 (14%)	0 (0%)	0.0316
Proportion of randomized wound pairs completely healed from baseline at Month 6[a] n (%)	7 (16%)	0 (0%)	0.0160

N: total number of observations; SD: Standard deviation; %: percentage.
Complete wound healing is defined as re-epithelialization with no drainage or erosion and presence of only minor crusting.
[a] The proportion of wounds achieving success criteria at Month 6 must have been confirmed at least 2 weeks later.
[b] One wound was excluded from the control group due to missing baseline value.

Practice Guidelines and Position Statements

European Reference Network for Rare Skin Diseases

The European Reference Network for Rare and Undiagnosed Skin Diseases published expert consensus clinical position statements in 2021 regarding practical recommendations for the management of patients suspected or diagnosed with

epidermolysis bullosa covering diagnosis, wound management, oral care and treatment of pain and itch. (5) They also published consensus clinical position recommendations in 2020 to aid decision-making and optimize clinical care by non-epidermolysis bullosa expert health professionals encountering emergency situations in babies, children and adults with epidermolysis bullosa. (9) Both consensus statements were published prior to the Food and Drug Administration (FDA) approval of beremagene geperpavec-svdt.

Dystrophic Epidermolysis Bullosa Research Association
International consensus best practice guidelines on skin and wound care in epidermolysis bullosa were published in 2017. (10) These guidelines were also published prior to the FDA approval of beremagene geperpavec-svdt.

National Instituted for Health and Care Excellence
A technology appraisal guidance titled "Beremagene geperpavec-svdt for treating skin wounds associated with dystrophic epidermolysis bullosa" is currently in the draft stage and is expected to be published in July 2026. (11)

Ongoing and Unpublished Clinical Trials
A currently ongoing or unpublished trial that might influence this policy is listed in Table 3.

Table 3. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT07016750[a]	A Study Assessing B-VEC Compared to Matching Placebo for the Treatment and Prevention of Corneal Abrasions in Dystrophic Epidermolysis Bullosa	16	Mar 2026
NCT04917887	Long-Term Follow-up Protocol	50	May 2028

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for

defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J3389, J3401

*Current Procedural Terminology (CPT®) ©2025 American Medical Association: Chicago, IL.

References

U.S. Food and Drug Administration Labels:

1. FDA – Vyjuvek (beremagene geperpavec-svdt) Highlights of Prescribing Information. U.S. Food and Drug Administration: Prescribing Information (09/2025). Available at accessdata.fda.gov (accessed November 14, 2025).
2. FDA – Zevaskyn (prademagene zamikeracel) Highlights of Prescribing Information. U.S. food and Drug Administration: Prescribing Information (04/2025). Available at accessdata.fda.gov (accessed January 8, 2026).

Others:

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4. Tidman MJ, Eady RA. Evaluation of anchoring fibrils and other components of the dermal-epidermal junction in dystrophic epidermolysis bullosa by a quantitative ultrastructural technique. J Invest Dermatol. May 1985; 84(5):374-377. PMID 4039741
5. Burgeson RE. Type VII collagen, anchoring fibrils, and epidermolysis bullosa. J Invest Dermatol. Sep 1993; 101(3):252-255. PMID 8370960
6. Dunnill MG, McGrath JA, Richards AJ, et al. Clinicopathological correlations of compound heterozygous COL7A1 mutations in recessive dystrophic epidermolysis bullosa. J Invest Dermatol. Aug 1996; 107(2):171-177. PMID 8757758
7. Vahidnezhad H, Youssefian L, Zeinali S, et al. Dystrophic Epidermolysis Bullosa: COL7A1 Mutation Landscape in a Multi-Ethnic Cohort of 152 Extended Families with High Degree of Customary Consanguineous Marriages. J Invest Dermatol. Mar 2017; 137(3):660-669. PMID 27899325
8. Fine JD. Epidemiology of Inherited Epidermolysis Bullosa Based on Incidence and Prevalence Estimates From the National Epidermolysis Bullosa Registry. JAMA Dermatol. Nov 01 2016; 152(11):1231-1238. PMID 27463098
9. Mellerio JE, El Hachem M, Bellon N, et al. Emergency management in epidermolysis bullosa: consensus clinical recommendations from the European reference network for rare skin diseases. Orphanet J Rare Dis. Jun 06 2020; 15(1):142. PMID 32505191
10. International consensus best practice guidelines skin and wound care in epidermolysis bullosa. Published 2017. Available at debra-international.org (accessed June 24, 2025).

11. National Institute for Health and Care Excellence. Beremagene geperpavec for treating skin wounds associated with dystrophic epidermolysis bullosa [ID3959]. Available at nice.org.uk (accessed February 17, 2026).

Centers for Medicare & Medicaid Services

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare & Medicaid Services does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at cms.hhs.gov.

Policy History/Revision

Date	Description of Change
5/7/2026	Document updated. The following change was made to Coverage: Added medically necessary language for prademagene zamikeracel (Zevaskyn™): Prademagene zamikeracel (Zevaskyn) may be considered medically necessary for the treatment of wounds in adult and pediatric individuals diagnosed with recessive dystrophic epidermolysis bullosaconditions when the following criteria are met. 1. The individual must have the following: a. Wounds associated with recessive dystrophic epidermolysis bullosa; 2. AND ALL the following: a. Documented biallelic pathogenic mutations in the collagen type VII alpha 1 chain (COL7A1) gene; b. Positive expression of the non-collagenous region 1 of the type 7 collagen protein (NC1+) in the skin; c. Presence of at least one chronic wound (e.g., stage 2 wounds that have an area ≥ 20 cm2) and have been present for at least 3 months; d. Presence of clinical manifestations of RDEB, such as extensive skin blistering, skin erosions, or scarring. Prademagene zamikeracel (Zevaskyn) is considered experimental, investigational and/or unproven for all other non-Food and Drug Administration approved indications. Added references 1, 2, 11; others updated or removed.
1/1/2026	New medical document.