Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

Medical benefit drug policies are a source for BCBSM and BCN medical policy information only. These documents are not to be used to determine benefits or reimbursement. Please reference the appropriate certificate or contract for benefit information. This policy may be updated and therefore subject to change.

P&T Date: 06/05/2025

Zevaskyn™ (prademagene zamikeracel)

HCPCS: J3590

Policy:

Requests must be supported by submission of chart notes and patient specific documentation.

A. Coverage of the requested drug is provided when all the following are met:
   a. Diagnosis of recessive dystrophic epidermolysis bullosa (RDEB) confirmed by genetic test results documenting mutations in the *COL7A1* gene
   b. Age ≥ 6 years old
   c. Wound sites requiring treatment must be open and meet ALL the following:
      i. Area must be ≥ 20 cm^2
      ii. Present for at least 6 months
      iii. Classified as a stage 2 wound, defined as partial thickness loss of dermis presenting as a shallow open ulcer with a pink or red wound bed, without slough or bruising
   d. Prescriber attestation that the member is receiving and adherent to standard wound care interventions
   e. Must not have current evidence or a history of squamous cell carcinoma or active infection in the area undergoing treatment
   f. Not to be used in combination on the same wound with other gene therapies for the treatment of RDEB
   g. The requesting physician attests to providing clinical outcome information within the appropriate provider portal as requested by BCBSM.
   h. Trial and failure, contraindication, OR intolerance to the preferred drugs as listed in BCBSM/BCN's utilization management medical drug list.

B. Quantity Limitations, Authorization Period and Renewal Criteria
   a. Quantity Limits: Align with FDA recommended dosing
   b. Authorization Period: Six months
   c. Renewal Criteria: Not applicable as no further authorization will be provided.

***Note: Coverage and approval duration may differ for Medicare Part B members based on any applicable criteria outlined in Local Coverage Determinations (LCD) or National Coverage Determinations (NCD) as determined by Center for Medicare and Medicaid Services (CMS). See the CMS website at http://www.cms.hhs.gov/. Determination of coverage of Part B drugs is based on medically accepted indications which have supported citations included or approved for inclusion determined by CMS approved compendia.

Background Information:

- Epidermolysis bullosa, or EB, is a rare, inherited connective tissue disorder that causes abnormalities in cohesion of layers of the skin. There are 4 different types of EB, one of which is dystrophic epidermolysis bullosa (DEB) which makes up about 25% of EB cases. DEB can be inherited dominantly or recessively, with recessive cases being the most common and most severe. Patients with dominant DEB have few complications and survive into adulthood, while those with recessive only live to their 3rd or 4th decade, often dying of squamous cell carcinoma or renal failure.

- DEB is caused by mutations in the *COL7A1* gene which codes for Type 7 collagen, whose responsibility is to bind the dermis to the epidermis. In DEB, Type 7 collagen is either reduced or completely absent, creating extremely fragile skin that blisters between the dermis and the epidermis and tears from even the most minor friction or trauma, such as holding a pencil or putting on a shirt. The constant cycle of blistering, wounding, and re-healing that occurs with DEB contributes to complications like infection, debilitating scarring, physical deformities, pubertal or growth delay, anemia, esophageal blistering, spinal fractures, and squamous-cell carcinoma.

- Clinical practice guidelines for laboratory diagnosis of epidermolysis bullosa developed on behalf of the Dystrophic Epidermolysis Bullosa Research Association (DEBRA) International (2020) recommend every patient with an established or suspected diagnosis of EB undergo genetic testing (level of evidence 2++, grade of recommendation B). Skin biopsy of an induced blister with immunofluorescence mapping (IFM) and/or transmission electron microscopy (TEM) may also be useful in the diagnosis of EB; however, with DEB, particularly in mild cases, the results of these tests may not deliver a useful result and genetic testing documenting the presence of mutations in the *COL7A1* gene would be required to deliver the final diagnosis.

- The goal of treatment is to promote wound healing, prevent infection and other complications, and protect the skin. Prior to the FDA approval of DEB therapies, there were no approved treatments for any form of EB. Management has historically been supportive, involving a multidisciplinary team that includes wound care, infection and pain control, nutritional support, and prevention and treatment of complications.

- A consensus statement from the European Reference Network for Rare Skin Diseases on the practical management of EB (2021) and an international consensus on best practice guidelines for skin and wound care in EB from Wounds International (2017) regard wound care as the cornerstone of treatment for EB patients. Skin and wound assessments should be undertaken regularly and management tailored to suit both the type of EB and the specific characteristics of the wound, as well as the needs and preferences of the patient. Regular follow up on patient and caregiver adherence to treatment should also be performed with adaptation of the care plan to meet the patient's needs and preferences, as needed.

    - Malnutrition, anemia, pruritus, and pain can compromise a patient's ability to heal; therefore, these conditions should be treated appropriately to optimize long-term wound healing and minimize further skin damage and trauma.

    - Atraumatic dressings should be utilized to prevent blistering and skin and wound bed damage. Dressing examples include polymeric membrane, super-absorbent, soft silicone mesh or foam, lipido-colloid, foam, and keratin. Most dressings should be changed every 1 to 3 days unless otherwise noted by the manufacturer or required by the patient's individual needs.

    - Preventative measures to avoid and/or reduce blister formation should also be enforced, such as padding trauma-exposed sites, avoidance of tight clothing, choosing suitable footwear with appropriate insoles and/or orthotics. Any intact blisters should be lanced and drained as they are not self-limiting.

    - Wound management in DEB must also address infection, critical colonization, and protection from additional trauma. Bacterial burden can be controlled by systemic or topical therapies.

    - Healing rate of wounds should be monitored by checking advancement of the wound edges. A reduction of 20-40% in 2 to 4 weeks may predict healing by 12 weeks. Pain and itch reduction and resolution of infection should also be evaluated.

- Recently approved treatments for DEB include topical gene therapy Vyjuvek® for the treatment of wounds in patients with DEB and mutations in the *COL7A1* gene, Filsuvez®, a topical gel that promotes general wound healing of DEB-associated wounds, and Zevaskyn, an autologous cell sheet-based gene therapy for the treatment of wounds in adults and pediatric patients with RDEB. All three products work locally to heal open skin wounds and do not treat extracutaneous manifestations of DEB; therefore, supportive and palliative care will continue to remain essential even in patients receiving treatment with FDA-approved therapies.

- Zevaskyn consists of a patient's own cells that have been gene-modified through retroviral vector (RVV) transduction to express the *COL7A1* gene to produce the collagen 7 (C7) protein. These cells are formed into cellular sheets for topical application onto wounds. It is the only FDA-approved product to treat RDEB wounds with a one-time surgical application. The use of Zevaskyn has not yet been addressed by any guidelines or consensus statements.

- The safety and effectiveness of Zevaskyn was established primarily in the pivotal, randomized, intrapatient-controlled Phase III VIITAL study, which compared Zevaskyn to standard of care (SOC) treatment in patients with RDEB wounds. Eligible patients were 6 years of age and older and required to have at least one pair of matched, large ($\geq$ 20 cm^2), chronic (open for $\geq$ 6 months) stage 2 wounds associated with RDEB. Stage 2 wounds are typically shallow with a reddish base and are characterized by partial-thickness skin loss into, but no deeper than, the dermis.

    - The matched wound pairs were randomized 1:1 to receive either Zevaskyn (up to 6 sheets) or control treatment consisting of SOC wound dressings and palliative care. Eleven patients ranging from 6 to 40 years old were enrolled and a total of 86 wounds were randomized to treatment.

    - The co-primary endpoints were the proportion of randomized wound pairs with at least 50% healing at 6 months with confirmation of wound healing two weeks later, and pain reduction as accessed by the mean differences in patient-reported pain scores using the Wong-Baker FACES® scale between randomized wound pairs at 6 months.

    - The trial met its co-primary endpoints. With Zevaskyn treatment, 81% of wounds (35/43) showed 50% or more healing at 6 months compared to 16% (7/43) in SOC-treated wounds. Additionally, Zevaskyn treatment demonstrated a nearly 3.5-times reduction in pain versus matched control wounds as reported following wound dressing changes using the Wong-Baker FACES pain rating scale (3.1-point reduction vs. 0.9-point reduction, respectively, utilizing a scale of 0-10; p=0.0002).

- Up to 12 Zevaskyn sheets may be manufactured per patient per treatment cycle, with each sheet covering an area of 41.25 cm^2. The recommended dose is based on wound surface area. Zevaskyn sheets are surgically applied to the wound(s) in a single surgical session at a qualified treatment center by a qualified healthcare provider and must not be trimmed. Only once Zevaskyn treatment cycle is recommended per treatment area. If different areas develop that necessitate treatment, a patient may then require more than one cycle.

- Additional gene and cell therapies are in development for the treatment of DEB. At present, there is no literature to support combination use of multiple gene therapies for the treatment of DEB

- Provider portals are used to capture clinical outcome information for patients on select high-cost treatments, such as gene and cellular therapies. If a patient meets medical necessity as defined by this policy and is approved for

treatment, the requesting physician must attest to providing clinical outcome information within the appropriate provider portal at the requested cadence.

References:

1. DEBRA International. EB in Depth. March 2021. Accessed April 30, 2025. Available at: https://www.debra.org/about-eb/eb-depth.
2. 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
3. Eichstadt S, Tang JY, Solis DC, Siprashvili Z, Marinkovich MP, Whitehead N, Schu M, Fang F, Erickson SW, Ritchey ME, Colao M, Spratt K, Shaygan A, Ahn MJ, Sarin KY. From Clinical Phenotype to Genotypic Modelling: Incidence and Prevalence of Recessive Dystrophic Epidermolysis Bullosa (RDEB). Clin Cosmet Investig Dermatol. 2019 Dec 24;12:933-942. doi: 10.2147/CCID.S232547. Erratum in: Clin Cosmet Investig Dermatol. 2021 Jun 21;14:679. PMID: 31920360; PMCID: PMC693531
4. Has C, Bauer JW, et al. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. Br J Dermatol. 2020 Oct;183(4):614-627. doi: 10.1111/bjd.18921. Epub 2020 Mar 11. PMID: 32017015
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. Has C, Liu L, et al. Clinical practice guidelines for laboratory diagnosis of epidermolysis bullosa. Br J Dermatol (2020); 182: 574-592.
7. IPD Analytics. Payer & Provider Insights. April 2025. Accessed April 30, 2025. https://www.ipdanalytics.com
8. Murrell DF. Overview of the management of epidermolysis bullosa. In: UpToDate. Shefner JM (Ed), UpToDate, Waltham, MA. (Accessed on April 30, 2025).
9. Zevaskyn [prescribing information]. Cleveland, OH; Abeona Therapeutics: April 2025.

<table>
<tr><td colspan="3">Policy History</td></tr>
<tr><td>#</td><td>Date</td><td>Change Description</td></tr>
<tr><td>1.4</td><td>Effective Date: 07/01/2025</td><td>UM medical management system update for MAPPO and BCNA
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>Yes</td></tr><tr><td>BCNA</td><td>Yes</td></tr></table></td></tr>
<tr><td>1.3</td><td>P&T Date: 06/05/2025

Effective Date: 07/21/2025</td><td>New policy.

This criteria replaces previously approved preliminary criteria.</td></tr>
</table>

<table>
<tr><td>1.2</td><td>Effective Date: 05/08/2025</td><td>UM medical management system update for BCBS and BCN
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>Yes</td></tr><tr><td>BCN</td><td>Yes</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table></td></tr>
<tr><td>1.1</td><td>Effective Date: 06/06/2024</td><td>Addition of criteria requiring attestation of adherence to standard wound care interventions to align with Vyjuvek criteria</td></tr>
<tr><td>1.0</td><td>Effective Date: 04/11/2024</td><td>Preliminary Drug Review
<table><tr><th>Line of Business</th><th>PA Required in Medical Management System (Yes/No)</th></tr><tr><td>BCBS</td><td>No</td></tr><tr><td>BCN</td><td>No</td></tr><tr><td>MAPPO</td><td>No</td></tr><tr><td>BCNA</td><td>No</td></tr></table></td></tr>
</table>

** The prescribing information for a drug is subject to change. To ensure you are reading the most current information it is advised that you reference the most updated prescribing information by visiting the drug or manufacturer website or http://dailymed.nlm.nih.gov/dailymed/index.cfm.*