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.

Effective Date: 06/06/2024

Vyjuvek™ (beremagene geperpavec)

HCPCS: J3401

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. FDA approved age
   b. Diagnosis of dystrophic epidermolysis bullosa (DEB) confirmed by genetic test results documenting mutations in the *COL7A1* gene
   c. Presence of open wounds requiring treatment
   d. Prescriber attestation that member is receiving and adherent to standard wound care interventions
   e. Patient 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 DEB
   g. 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: Clinical documentation must be provided to confirm that current criteria are met and that the medication is providing clinical benefit

***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 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 Vyjuvek, 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, pruritis, 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.

- Vyjuvek was approved by the FDA for the treatment of wounds in patients 6 months of age and older with DEB with mutations in the *COL7A1* gene. It is the first FDA-approved treatment for any type of EB, and the first non-invasive, topical, and redosable gene therapy approved by the FDA. Unlike most other gene therapies, Vyjuvek is "off the shelf", meaning therapy does not need to be made from the patient's own cells so the patient does not have to wait for the drug to be manufactured prior to initiating therapy. Because Vyjuvek works locally at the site of application, it should be used in addition to standard of care wound management and supportive/palliative care for DEB. The use of Vyjuvek has not yet been addressed by any guidelines or consensus statements.

- Vyjuvek utilizes an engineered herpes simplex virus vector virus to deliver two copies of functional *COL7A1* genes to affected cells when applied directly to the wound. Upon application, the patient's skin cells take up the genetic code housed in the vector virus and use it to produce functional COL7A1 protein. This protein assembles into anchoring fibrils, or Type 7 collagen, which holds the dermis and epidermis together to prevent and minimize blister formation between the skin layers.

- The safety and effectiveness of Vyjuvek was established primarily in the Phase III, multicenter, randomized, double-blind, placebo-controlled, intra-patient GEM-3 trial. Eligible patients were required to have a clinical diagnosis of DEB, characterized by blistering, wounds, and scarring, and confirmed by genetic testing. Patients were also required to have two cutaneous wounds similar in size, appearance, and anatomical regions. One wound from each pair was treated with Vyjuvek and the other treated with placebo. Wound sites with current evidence or history of squamous-cell carcinoma or active infection were excluded as sites for application of Vyjuvek or placebo.

    - Of the 31 patients enrolled in the trial, one had a dominant DEB genotype while the remaining 30 had a recessive DEB genotype. The age of the trial population ranged from 1 year to 44 years old.

    - Patients were randomized to once-weekly treatment with Vyjuvek or placebo until wound closure over a 6-month treatment period. Once a wound closed, product application was omitted, but if a healed wound reopened at any point in the study, then weekly application was resumed.

    - The primary efficacy endpoint was complete wound healing at weeks 22 and 24 or weeks 24 and 26, defined as 100% wound closure from exact wound area at baseline evaluated at two consecutive visits two weeks apart. Efficacy was further supported by the secondary endpoint of complete wound healing at weeks 8 and 10 or weeks 10 and 12.

    - Vyjuvek met its primary endpoint, with 65% of Vyjuvek-treated wounds achieving complete wound healing at 6 months compared to only 26% of placebo-treated wounds (p=0.012). Secondary endpoint was also met, with 68% of Vyjuvek-treated wounds achieving complete wound healing at weeks 8 and 10 or weeks 10 and 12 compared to 23% of placebo-treated wounds (p=0.003).

- Vyjuvek gel must be prepared at the pharmacy by mixing the Vyjuvek biological suspension into the excipient gel for immediate use within 8 hours of mixing, and application should only be performed by a healthcare professional. The gel should be applied to wounds until they are completely closed before selecting new wounds to treat. Should previously treated wounds re-open, their weekly treatment should be prioritized per the prescribing information.

- 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.

References:

1. Marinkovich MP, Gonzalez ME, et al. (2022, March 25-29). GEM-3: A Phase 3 Study of Beremagene Geperpavec (B-VEC), an Investigational Topical Gene Therapy, for the Treatment of Dystrophic Epidermolysis Bullosa (DEB). 2022 American Academy of Dermatology Annual Meeting. Boston, MA, United States. https://ir.krystalbio.com/static-files/bb74b04e-7e3d-44f8-afda-5469a3cf16b4
2. IPD Analytics. Payer & Provider Insights. November 2022. Accessed November 1, 2022. https://www.ipdanalytics.com.
3. Guide SV, Gonzalez ME, et al. Trial of Beremagene Geperpavec (B-VEC) for Dystrophi Epidermolysis Bullosa. N Engl J Med 2022; 387:2211-9.
4. Has C, Liu L, et al. Clinical practice guidelines for laboratory diagnosis of epidermolysis bullosa. Br J Dermatol (2020); 182: 574-592.
5. Bruckner AL and Murrell DF. Diagnosis of epidermolysis bullosa. In: UpToDate. Shefner JM (Ed), UpToDate, Waltham, MA. (Accessed on November 1, 2022).
6. Murrell DF. Overview of the management of epidermolysis bullosa. In: UpToDate. Shefner JM (Ed), UpToDate, Waltham, MA. (Accessed on November 1, 2022).
7. Denyer J, Pillay E, Clapham J. Best practice guidelines for skin and wound care in epidermolysis bullosa. An International Consensus. Wounds International, 2017.
8. 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.
9. Vyjuvek [prescribing information]. Krystal Biotech, Inc.: Pittsburgh, PA; May 2023.
10. 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.
11. 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: May 2, 2024.

<table>
<tr><th colspan="3">Policy History</th></tr>
<tr><th>#</th><th>Date</th><th>Change Description</th></tr>
<tr><td>1.4</td><td>Effective Date: 06/06/2024</td><td>Added criteria requiring attestation of adherence to standard wound care measures and prevention of concomitant use with other DEB gene therapies</td></tr>
<tr><td>1.3</td><td>Effective Date: 08/14/2023</td><td>UM medical management system update for BCNA and MAPPO
<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>1.2</td><td>Effective Date: 08/10/2023</td><td>New policy. This criteria replaces previously approved preliminary criteria</td></tr>
<tr><td>1.1</td><td>Effective Date: 06/15/2023</td><td>UM medical management system update for BCN and BCBS
<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>1.0</td><td>Effective Date: 12/01/2022</td><td>Preliminary drug review</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.*