Molina Clinical Policy
Vyjuvek (beremagene geperpavec): Policy No. 439

Last Approval: 6/14/2023
Next Review Due By: June 2024

DISCLAIMER

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. Policies are not a supplementation or recommendation for treatment; Providers are solely responsible for the diagnosis, treatment, and clinical recommendations for the Member. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (e.g., will be paid for by Molina) for a particular Member. The Member's benefit plan determines coverage – each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their Providers will need to consult the Member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a Member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid Members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP and provide the directive for all Medicare members. References included were accurate at the time of policy approval and publication.

OVERVIEW

Epidermolysis bullosa (EB) is one of several genetic dermatologic disorders associated with skin fragility. In general, these are associated with skin blistering; EB is the classical prototype. In recent years, several new gene associations and clinical subtypes have been identified. The spectrum of disease was reclassified by consensus expert review in 2020 considering clinical and molecular data, both genotype and phenotype. Initial classification models were based upon the level of skin cleavage which led to many of the physically identifiable phenotypic characteristics. The definitive physical manifestations are peeling, blistering, erosions, ulcerations, and wounds. The spectrum of severity can range from minor skin findings to lethal disorders. Newer classification schema focus on molecular data when known. There are four major classical types of EB-EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB) and Kindler EB (KEB) in addition to EB related disorders. DEB has three subtypes, a dominant and a recessive form. The recessive form is more severe and caused by mutations in the collagen gene COL7A1. Type VII collagen helps bind the dermis to the outer epidermis at the basement membrane. While initial diagnosis is typically clinical due to visible manifestations, subsequent biopsy, immunofluorescence, and molecular genetic diagnosis is used for prognostication, treatment, and planning purposes (Has, 2020).

DEB is caused by mutations in COL7A1, a gene which encodes type VII collagen. Autosomal recessive DEB is caused by mutations in both alleles. Many novel mutations have been identified in the COL7A1 gene (Järvikallio, 1997). Attempts to modulate the production of type VII collagen have been proposed to treat DEB. Beremagene geperpavec (B-VEC) is a novel topical gene therapy for the treatment of DEB to assist in production of type VII collagen.

B-VEC is a patented topically applied gel that contains a non-integrating, replication-incompetent herpes virus (HSV-1) which expresses the human collagen VII protein. The recombinant herpes simplex viral vector genome has a transgene which encodes a collagen alpha 1 chain polypeptide (Krishnan, 2018). While members were more likely to achieve complete wound healing, when exposed to B-VEC compared to placebo, the long-term effects and durability of response as well as side effects provided the topical and directed nature of this therapy are unknown (Guide, 2022).

COVERAGE POLICY

Vyjuvek (beremagene geperpavec) for the treatment of DEB may be considered medically necessary when **ALL** the following criteria with are met with relevant documentation:

1. A diagnosis of recessive DEB (confirmed by immunofluorescence, electron microscopy, or antigen mapping); **AND**
2. Evidence of biallelic COL7A1 gene mutation; **AND**
3. Evidence of clean, non-infected wound, with adequate granulation tissue and excellent vascularization; **AND**
4. Member has not received, or is being considered for other gene therapy, or investigational cellular therapy; **AND**

5. Member is receiving standard of care wound therapy; **AND**
6. Member is not on chemotherapy or immunotherapy; **AND**
6. Member is not pregnant or lactating; **AND**
7. Member does not have squamous cell carcinoma (or have a history of) in affected area; **AND**
8. Member does not have an active drug or alcohol addiction or hypersensitivity to local anesthesia; **AND**
9. Member has not had a recent skin graft (past three months); **AND**
10. Member has no evidence of immune response to COL7 by immunofluorescence (no history of anti-COL7 antibodies at baseline); **AND**
11. Dose below FDA (Food and Drug Administration) maximum dose; **AND**
12. Member is age ≥ 6 months.

LIMITATIONS AND EXCLUSIONS

There are no contraindications listed in the manufacturer's labeling at this time.

The following are considered **experimental, investigational, and unproven** based on insufficient evidence:
1. Any indications other than those listed above.
2. Treatment beyond 26 weeks.

PRESCRIBER REQUIREMENTS: Prescribed by or in conjunction with a board-certified dermatologist, geneticist, or dermatopathologist.

AGE RESTRICTIONS: Age ≥ 6 months

DOSING CONSIDERATIONS: All doses must be administered by healthcare personnel

Age Range	Maximum Weekly Dose (plaque forming units; PFU)	Maximum Weekly Volume (milliliter; mL)*
6 months to <3 years old	1.6×10^9	0.8
≥ 3 years old	3.2×10^9	1.6

*Maximum weekly volume is the volume after mixing VYJUVEK biological suspension with excipient gel.

Wound Area (cm^2)*	Dose (PFU)	Volume (mL)
<20	4×10^8	0.2
20 to <40	8×10^8	0.4
40 to 60	1.2×10^9	0.6

*For wound area over 60 cm^2, recommend calculating the total dose based on this table until the maximum weekly dose is reached.

MONITORING PARAMETERS: Member should be monitored according to FDA-approved labeling and best practice.

CONTINUATION OF THERAPY: Treatment beyond 26 weeks has not been completely studied and will not be authorized.

DOCUMENTATION REQUIREMENTS. Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational, or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

SUMMARY OF MEDICAL EVIDENCE

The FDA approval of B-VEC was based on Phase I and Phase II clinical studies and a subsequent double-blind, multicenter, intrapatient randomized, placebo-controlled Phase III trial (NCT04491604). The study titled "A Phase III Efficacy and Safety Study of Beremagene Geperpavec (B-VEC, Previously "KB103") for the Treatment of Dystrophic Epidermolysis Bullosa (DEB)" with results as noted below (Guide, 2022).

Phase 3 Trial. All patients involved had genetically confirmed recessive DEB. For each enrolled patient, a primary matched wound pair was selected. The wounds were matched in size, region, and appearance and randomly assigned to receive either weekly application of B-VEC or placebo for 26 weeks. Members were studied beginning in August 2020 with a primary completion date of October 2021. Patients were compared for primary and secondary end points.

Primary Outcome Measure: Primary wound with complete wound healing of treated versus untreated wounds at weeks 22 and 24 or weeks 24 and 26.

Secondary Outcome Measures: Complete wound healing compared to baseline at week 12. Additionally, changes in visual analog scale (VAS) or Faces (FLACC-R) pain scores during dressing changes from baseline at weeks 22, 24, and 26 were recorded. The proportion of primary wound sites with >75% healing compared to baseline using Canfield photography quantitation at 24 weeks post baseline was measured as well as relative time to wound closure. However, this was changed and resubmitted on January 25, 2023. Complete wound healing at week 8 and 10 or complete healing at weeks 10 and 12 were assessed.

Relative time to wound closure from baseline and duration of closure were also both measured.

Results. A total of 31 patients were evaluated and started treatment. Patients were eligible if they were aged six months or older with a clinical diagnosis of DEB and confirmation by genetic testing for COL7A1. Recipient patients needed to have two cutaneous wounds that were similarly matched in size, anatomical region, and appearance. Wounds could not appear infected and were notably clean with adequate granulation and vascularization. Patients were excluded if they had history or current evidence of squamous cell carcinoma in the treatment area or if they were on chemotherapy or immunotherapy. Patients with hypersensitivity to local anesthesia, those who had a prior skin graft in the past three months, or those with inability to travel were excluded. Also excluded were those who had drug or alcohol addiction or other interfering conditions.

31 patients started the study; 3 subjects withdrew from it. Of the 31 participants, the mean age was 17.2 years with a standard deviation of 10.7 years. Ten of the patients studied were age $\leq$ 12 and 12 patients were over age 18. Of those patients, 11 (35.5%) were female and 20 (64.5%) were male. The ethnicity of of participants 16/31 (51.6%) were Hispanic or Latino and the rest were not. Race was White 20/31 (64.5%), 6/31 (19.4%) Asian, and 5/31 American Indian or Alaskan Native. The primary wound area was 14.35 cm^2 with a standard deviation of 12.69cm^2. For members treated with B-VEC 20.9/31 wounds achieved complete healing opposed to 6.7/31 placebo treated wounds. This outcome was statistically significant with a p value of 0.00192. Of note a multiple imputation approach was used for missing data.

In review of secondary outcomes, primary wound healing occurred between weeks 8 and 10 or 10 and 12 for 21.9/31 of study treated patients versus 6.1/31 placebo treated patients. This was statistically significant with a p value of 0.00047 again using multiple imputation approach for missing data. Pain scores were only reported for subjects aged 6 or older and hence 27 participants noted pain score measurements on a standard 0-10 score. At weeks 22, 24, and 26 B-VEC treated patients experienced pain scores of 2.346, 2.325, and 2.123 which represented a change of -0.88, -0.64, and -0.63 respectively. Placebo treated wounds at weeks 22, 24, and 26 experienced pain scores of 2.476, 2.548, and 2.871 which represented a change of -0.71, -0.08, and -0.38, respectively.

Adverse events were measured noting no mortality during the study. Serious adverse events were observed in 3/31 (9.68%) of participants and included severe anemia, diarrhea, cellulitis, and positive blood cultures. Other adverse events occurred in 54.84% of patients, the most common being chills, squamous cell carcinoma, and pruritus.

CODING & BILLING INFORMATION

HCPCS (Healthcare Common Procedure Coding System) Code

HCPCS	Description
C9399	Unclassified drugs or biologicals [when specified as Vyjuvek (beremagene geperpavec)]

CODING DISCLAIMER. Codes listed in this policy are for reference purposes only and may not be all-inclusive. Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement. Listing of a service or device code in this policy does not guarantee coverage. Coverage is determined by the benefit document. Molina adheres to Current Procedural Terminology (CPT®), a registered trademark of the American Medical Association (AMA). All CPT codes and descriptions are copyrighted by the AMA; this information is included for informational purposes only. Providers and facilities are expected to utilize industry standard coding practices for all submissions. When improper billing and coding is not followed, Molina has the right to reject/deny the claim and recover claim payment(s). Due to changing industry practices, Molina reserves the right to revise this policy as needed.

APPROVAL HISTORY

6/14/2023 New policy. Independent Review Organization Peer Review on June 1, 2023 by a practicing, board-certified physician with a specialty in Dermatology.

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