Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCTOP044.0624	**TOPICAL PRODUCTS** **TOPICAL AGENTS FOR EPIDERMOLYSIS BULLOSA** **Filsuvez®** (birch triterpenes 10% topical gel) **Vyjuvek®** (beremagene geperpavec-svdt gel)
Effective Date: 8/1/2024	**Review/Revised Date**: 05/24 (JCN)
Original Effective Date: 10/23	**P&T Committee Meeting Date**: 08/23, 06/24
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicare Part B
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA)-Approved Indications

Coverage for Medicaid is limited to a condition that has been designated a covered line-item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services when all applicable indication-specific criteria below are met. The Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit provides comprehensive and preventive health care services for children and adolescents up to their 21st birthday who are enrolled in Medicaid. Management of unfunded conditions falls under this benefit when they impact the ability to grow, develop or participate in school and the applicable indication-specific criteria below are met.

REQUIRED MEDICAL INFORMATION:
Initial authorization requires all the following be met:
1. One of the following:
    a. For Vyjuvek: Diagnosis of dystrophic epidermolysis bullosa (EB)
    b. For Filsuvez: Diagnosis of dystrophic EB or junctional EB
2. Confirmed diagnosis by genetic testing. For dystrophic EB, mutations in the collagen type VII alpha 1 chain (*COL7A1)* gene. For junctional EB, autosomal recessive mutations in the laminin-332 genes (LAMA3, LAMB3, LAMC2). Note:

other genes that can be involved include COL17A1, LAMA3A, ITGA6, ITGB4, ITGA313
3. Treatment will be used on a cutaneous wound (or wounds) that are clean in appearance with adequate granulation tissue, excellent vascularization, and do not appear infected
4. Dosing is within FDA-labeled guidelines

Reauthorization requires all the following be met:
1. Documentation of successful response to therapy as indicated by complete wound healing or decrease in wound size
2. Patient continues to have incomplete wound closures that are clean in appearance with adequate granulation tissue, excellent vascularization, and do not appear infected
3. Dosing is within FDA-labeled guidelines

EXCLUSION CRITERIA:
1. Skin graft within the past three months
2. Current evidence or a history of squamous cell carcinoma in the area(s) that will undergo treatment
3. Combination therapy with Vyjuvek and Filsuvez

AGE RESTRICTIONS:
May be approved for patients aged six months and older

PRESCRIBER RESTRICTIONS:
Must be prescribed by, or in consultation with, a with a dermatologist or provider with experience in treating epidermolysis bullosa

COVERAGE DURATION:
- For Filsuvez: Initial authorization will be approved for three months. Reauthorization will be approved for one year.
- For Vyjuvek: Initial authorization will be approved for six months. Reauthorization will be approved for one year.

QUANTITY LIMIT:
Filsuvez: 23.4 gram/day (1 single-use tube per day)
Vyjuvek: Four vials (10 mL) per 28 days

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy

document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION: Beremagene geperpavec (Vyjuvek®) is a topical HSV-1 vector based gene therapy that delivers functional *COL7A1* genes to both keratinocytes and fibroblasts. Expression of *COL7A1* leads to secretion of type VII collagen. Type VII collagen is a major component of the anchoring fibrils which hold the dermis and epidermis together. Individuals with dystrophic epidermolysis bullosa (DEB) have lower than normal or no functional anchoring fibrils[1].

Beremagene geperpavec does not prevent new wounds from occurring and continued application may be necessary to maintain effect. As local acting gene therapy, patients may require intermittent or ongoing therapy throughout their life[4,5]. It is possible for decreased requirements over time as wounds heal and stabilize.

Filsuvez® (birch triterpenes 10% topical gel) is a botanical derived from birch bark and includes a mixture of triterpenes such as betulin, lupeol, betulinic acid, erythrodiol, and oleanolic acid. It is thought that birch triterpenes work by accelerating wound healing through modulation of inflammatory mediators and enhancement of keratinocyte migration and differentiation.[15]

FDA APPROVED INDICATIONS:
Vyjuvek - Treatment of wounds in patients six months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the *collagen type VII alpha 1 chain (COL7A1)* gene

Filsuvez - Treatment of wounds in patients six months of age and older with dystrophic and junctional epidermolysis bullosa

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POSITION STATEMENT:
Epidermolysis bullosa (EB) is a rare genetic connective tissue disorder characterized by fragile and blistering skin and mucosal membranes. Significant scaring can occur which can lead to complications such as difficulty swallowing, fusion of skin between fingers and toes, joint deformities and vision loss[7].

There are many variations of EB, which are classified into four major types. These types are then further classified into subtypes[7]. Beremagene geperpavec (Vyjuvek®) is approved for treatment of wounds in individuals with dystrophic epidermolysis bullosa (DEB) only. Filsuvez® (birch triterpenes 10% topical gel) has been approved for treatment of wounds in both DEB and junctional EB (JEB). Genetic testing is recommended for diagnosis of EB and corresponding type.[13]

- Dystrophic epidermolysis bullosa – recessive (RDEB) (more severe form) or dominant (DDEB)
    - Caused by mutations in the type VII collagen (*COL7A1*) gene leading to reduced or absent levels of type VII collagen.
    - Individuals with DEB have lower than normal or no functional anchoring fibrils which are required for maintaining the integrity of the skin.
    - Skin cleavage occurs below the basement membrane within the superficial dermis
    - Prevalence of RDEB in the US is estimated around 1.4 per million with an incidence of 3.1 per million[6]
    - Prevalence of DDEB is approximately 1.5 per million with an incidence of 2.1 per million[6]
- Junctional epidermolysis bullosa (JEB) – is recessively inherited with two major subtypes, intermediate and severe (Herlitz JEB)[9]
    - Can involve several different mutations that affect the skin components in the basement membrane zone (skin cleavage occurs within the lamina lucida)[13,15]
    - Most often caused by mutations in the genes encoding for the protein laminin-323 (LAMA3, LAMB3, LAMC2)[15]
    - Other genes that can be involved include *COL17A1, LAMA3A, ITGA6, ITGB4, ITGA3*[13]
- Kindler epidermolysis bullosa (KEB)
- Epidermolysis bullosa simplex (EBS)
    - Most common type with estimated prevalence of 6 per million[6]

Depending on subtype, symptoms can range from mild (e.g., blistering to hands, feet, knees, elbows with normal life expectancy) to severe (e.g., death during infancy due to complications such as sepsis, dehydration, obstructive airway, electrolyte imbalances). Individuals are also at an increased risk of squamous cell carcinoma.

Management of epidermolysis bullosa is currently primarily supportive care including wound care, pain management, infection control and nutritional support. Management also includes prevention and treatment of complications[7]. Beremagene geperpavec (Vyjuvek®) was the first FDA-approved pharmacologic treatment of wounds associated with DEB. Filsuvez is the first FDA-approved therapy for the treatment of wounds associated with JEB and the second agent approved for DEB. Some standard care therapies for EB include:

- Reducing skin friction
- Keeping skin cool
- Daily skin care and dressings
- Managing blisters (not self-limiting)
- Addressing nutritional deficiencies
- Monitoring for skin cancer

The European Reference Network for Rare Skin Diseases (ERN-Skin) have put out recommendations for emergency management in EB for both in home and hospital care. Topics include sepsis, feeding inability in infants, esophageal obstruction, upper airway obstruction, urinary retention and corneal erosion[8]. ERN-Skin has also published practical recommendations for the diagnosis and management of the most common clinical issues in EB: skin blisters and wounds, oral manifestations, pain and itch.[11] Clinical practice guidelines for specific areas of care for individuals with EB such as anemia, pain, skin and wound and psychosocial have been developed are on available from the EB patient advocacy and support Network, Dystrophic Epidermolysis Bullosa Research Association (DEBRA) International website.[10]

Approval for Vyjuvek® was based on a phase 3 randomized, double blind, intrapatient placebo controlled trial of 31 patients with dystrophic epidermolysis bullosa. At 6 months, complete wound healing occurred in 67% of wounds exposed to Vyjuvek® compared to 22% with placebo. Absolute difference 38.7% (13.9-63.5) 95% CI p=0.012[4].

- Patient population: Patients (N=31) six months and older with dystrophic epidermolysis bullosa characterized by blistering, wounds and scarring and genetically confirmed mutations in the *COL7A1* gene.
    - Key exclusion criteria: current treatment with immunotherapy, chemotherapy or other investigational products; skin graft within past three months; wounds with current or history of squamous-cell carcinoma or active infection were excluded from being application sites.

- Intervention: For each patient, a primary wound pair was selected. Wounds were matched for size, region and appearance (i.e., wounds were clean with adequate granulation tissue, excellent vascularization and did not appear infected).
    - Wounds within each pair were assigned 1:1 to weekly application of either beremagene geperpavec (B-VEC) or placebo
- Baseline characteristics: 30 participants with RDEB and 1 with DDEB, median age 16 years with range 1-44
- Primary endpoint: complete wound healing
    - Defined as 100% wound closure as indicated by skin re-epithelialization without drainage, confirmed at two consecutive study visits two weeks apart (assessed at Weeks 22 and 24 or at Weeks 24 and 26)
- Efficacy:
    - 20 of 31 wounds exposed to B-VEC and 8 of 31 wounds exposed to placebo met the primary end point. Absolute difference of 38.7% (13.9-63.5) 95% CI, p=0.012.
    - Durability, which was defined as complete wound healing at both 3 and 6 months, was seen in 50% of wounds exposed to B-VEC and 7% of those exposed to placebo (difference of 43%; 95% CI, 23 to 63).
- Safety:
    - Most frequent adverse reactions (incidence >5%): pruritis, chills, erythema, rash, cough, and rhinorrhea
    - Warnings and precautions: Accidental exposure - avoid direct contact with treated wounds and dressings of treated wounds for approximately 24 hours following application. Clean the affected area if accidental exposure occurs.
    - Pharmacokinetic data suggest a lack of systemic exposure after topical application

Study limitations include that only one participant with DDEB was included in the trial and most wounds exposed to B-VEC were less than 20 cm^2 meaning efficacy or time to complete wound healing could differ for larger wounds.

Vyjuvek® is a biological suspension mixed into an excipient gel by a specialty pharmacy. Gel droplets are applied to wound(s) once weekly. Package labeling states that only a healthcare professional should apply Vyjuvek® either in a professional setting or in the home. The dose is dependent on the wound size with a maximum weekly volume based on age.

Dosing tables[1]

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.

Filsuvez® approval was based on the Phase 3 randomized, double-blind, vehicle-controlled EASE trial of 233 patients with DEB or JEB. Two phases, a 90-day double-blind phase and a 24-month open-label phase. Of those patients treated with Filsuvez, 41.3% achieved complete target wound closure within 45 days compared with 28.9% in the placebo control group (P = 0.013). However, key secondary endpoints were not met, including complete wound closure at 90 days compared to placebo.

- Patient population: Patients 6 months of age and older with DEB (n=175 for recessive DEB, n=20 dominant DEB) or JEB (n=26). Median age was 12 years.
    - Key exclusion criteria: EBS subtype, target wound ≥ 9 months old or signs of local infection, prior stem cell transplant or gene therapy for treatment of EB, current or former skin cancer
- Intervention: One wound was selected as the target wound for the primary efficacy endpoint. Target wounds were of partial thickness (wound that does not extend past the dermis layer) between 10 to 50 cm^2 in size and present for 21 days to 9 months. 1 mm of the gel was applied to wounds with each dressing change (every 1-4 days) for 90 days. Stratification by EB subtype and target wound size.

- Primary endpoint: Proportion of patients with first complete closure of target wound by Day 45 of the 90-day double-blind phase of the study.
    - complete wound closure was defined as skin re-epithelialization without drainage.
- Secondary endpoints: Time to first complete closure of target wound until Day 90, proportion of patients with first complete closure of target wound at Day 90, incidence of target wound infection between baseline and Day 90, maximum severity of target wound infection between baseline and Day 90, change from baseline in total body wound burden at Day 90, change from baseline in itching before wound dressing changes at Day 90
- Efficacy:
  Table 1: Efficacy results for the treatment of partial thickness target wounds in patients with EB[14,15]

Efficacy parameter	**Filsuvez** (n=109)	**Placebo** (n=114)	95% CI for treatment difference
Primary Endpoint: Proportion with first complete target wound closure at Day 45	41.3%	28.9%	(0.8, 25.6)
By EB type			
RDEB (n=175)	44%	26.2%	(3.9, 31.6)
DDEB (n= 20)	50%	50%	(−47.8, 47.8)
JEB (n=26)	18.2%	26.7%	(−40.4, 23.5)
Key secondary endpoint: Proportion with first complete target wound closure at Day 90	50.5%	43.9%	(−6.2, 20.0)

- Safety: Application site reactions in 7.3% of study subjects (vs. 6.1% in placebo)

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