Pharmacy Focus:
Emerging Treatments for Epidermolysis Bullosa

Key Takeaways

- Epidermolysis Bullosa is a rare genetic disease resulting in skin fragility and blistering.
- The standard of care treatment options have historically been limited supportive care, but now there are two FDA-approved therapies: Vyjuvek™ and Filsuvez®.
- High-cost gene and cell-based therapies are the focus of treatment expansion for Epidermolysis Bullosa.
- The annual cost of Vyjuvek varies by patient based on the number and size of open wounds, but it can exceed $1.2 million per year.

Epidermolysis Bullosa Overview and Current Treatment[1–9]

Epidermolysis Bullosa (EB) is a rare genetic disorder that creates fragility of the skin. Gene mutations alter the proteins that bind skin cells together, and there is a disruption in the basal layer of the epidermis that results in sores, blisters and tears that can even be present inside the body.

The prevalence (existing cases) of recessive and dominant dystrophic epidermolysis bullosa is estimated to be 1 in every 125,000 people, while the incidence (new cases) of any type of EB is estimated to occur in 1 of every 50,000 live births.

There are four major types of EB (though several associated subtypes have more than 30 types identified). The diagnosis depends on the gene mutation and the location of the skin changes. Location is based on the layer of skin, named top to bottom: epidermis, basement membrane, dermis and subcutaneous tissue (fat). The most common type of EB is epidermolysis bullosa simplex, and the rarest type is Kindler syndrome.

Below is a brief overview of the genes involved in each type of EB and the location where each type presents.

Type	Abbreviation	Impacted Genes	Affected Location
Epidermolysis bullosa simplex	EBS	Keratin genes KRT5 and KRT14	Lower part of the epidermis
Junction epidermolysis bullosa	JEB	Laminin-332 genes	Top portion of the basement membrane
Dystrophic epidermolysis bullosa (recessive and dominant)	DEB; RDEB; DDEB	Type VII collagen coding gene COL7A1	Upper dermis
Kindler syndrome	KS	Adhesion protein coding gene FERMT1	Multiple skin layers

Unfortunately, there is no cure for epidermolysis bullosa, but it is a growing area of investigation for new pharmacological therapies. Care usually consists of therapies that would prevent or control symptoms, including pain, itching, blisters, wounds and infections. Nutrition also may be addressed, and recommendations for supportive care can include cold water baths, soft clothing, lotions/creams/ointments and mittens at bedtime.

Skin and wound care also may include bathing in salt water (isotonic saline) to reduce pain or whirlpool therapy as an adjunct. Additionally, wound dressings, specifically nonstick or nonadherent silicone dressings and foam dressings, can be used.

Filsuvez® (birch triterpenes) 10% topical gel, a sterile botanical drug product, was approved in December 2023 for dystrophic and junctional epidermolysis bullosa in those over the age of six months. Filsuvez is applied at wound dressing changes for partial thickness wounds, which are wounds that do not extend past the skin's dermis layer. During the EASE trial, treatment was applied to target wounds every one to four days for 90 days. The primary endpoint was the proportion of subjects with first complete closure of target wounds by Day 45 of the 90-day double-blind phase of the study in treated versus placebo groups. Results showed 41.3 percent of subjects having complete closure of target wounds within 45 days versus 28.9 percent of subjects who received placebo gel. The mechanism that Filsuvez works for EB is unknown, but it is thought to promote general wound healing by activating certain skin cells in the epidermis called keratinocytes. The average wholesale price (AWP) for one 25ml (23.4g) tube is $2,160.

On May 19, 2023, the FDA approved Vyjuvek™ (beremagene geperpavec), a topical gene therapy, for those with dystrophic epidermolysis bullosa six months in age or older with mutations of the collagen type VII alpha 1 chain (COL7A1) gene. It will be the focus of further discussion in the next section.

Epidermolysis Bullosa Treatment/Management Options[1–3, 9]

Drug/ Intervention	Dosing	How It Works	Price	Adverse Events	EB Population
Supportive Care	Individualized to the patient	Wound care; infection control; nutritional support	Depends on severity; care may require inpatient care, which may be higher in price	Depends on care needed	All
Vyjuvek™ Topical Gel (J3401)	6 months to 3 years of age: 1.6 x 10^9 PFU max weekly dose ≥ 3 years old: 3.2 x 10^9 PFU max weekly dose	HSV-1 vector-based gene therapy	About $631,000 per year ($24,250 per vial)	Itching, chills, redness, cough, rash, and runny nose	DDEB/RDEB
Filsuvez® 10% Topical Gel (birch triterpenes) (Rx)	1mm layer to affected wound surface with wound dressing	Botanical product, unknown mechanism	AWP $2,160 per single-use 23.4g tube	Application site reactions	JEB DDEB/RDEB

Therapy Spotlight: Vyjuvek™ (beremagene geperpavec-svdt)[5, 10–12]

Vyjuvek (beremagene geperpavec-svdt) is a herpes-simplex virus type 1 (HSV-1) vector-based gene therapy. Those who are over the age of six months, diagnosed with dystrophic epidermolysis bullosa (DEB) and have mutations in the COL7A1 gene may be considered for this topical gel. Vyjuvek is the first gene therapy for DEB to be approved by the FDA. The goal of this medication is to address the disease at a gene level rather than just working to control symptoms. To accelerate wound healing, the gene therapy will provide the COL7A1 gene that is mutated in individuals with this disease.

A randomized, double-blinded, placebo-controlled study evaluated both the safety and efficacy of Vyjuvek. This study included 31 individuals, and two wounds per patient were assessed. The results of the study looked at the proportion of full, 100 percent wound closure after six months of treatment. At the close of the study, 65 percent of the patients who received treatment with Vyjuvek achieved full closure of their wounds, compared with 26 percent of those receiving the placebo.

Vyjuvek is applied to the wound once a week and spaced evenly on the wound. There are certain dosing recommendations based on the size (cm) of the wound area. The gel is applied by a health care provider in a professional setting. It is important to avoid direct contact with treated wounds for about 24 hours after Vyjuvek is applied.

There is a maximum weekly recommended dose of 1.6ml across all wounds. Based on use in clinical trials, it is estimated that the average patient will use 26 vials per year after an 18-to-24-month induction period, which calculates to a wholesale acquisition cost (WAC) of $630,500 annually. However, the annual cost will vary by patient based on the surface area of wounds, the number of open wounds and the length of the induction period needed for the patient to reach a steady cycle of closure and reopening. The annual WAC for patients that require application every week is $1,261,000.

Treatments in the Pipeline[6, 9, 12]

Abeona Therapeutics' Pz-cel/EB-101 (prademagene zamikeracel) was set for approval May 15, 2024, but the company received a complete response letter from the FDA, delaying approval until additional manufacturing specifics are submitted. A new potential approval date has not been set but will likely not be until late 2024 or early 2025.

This one-time treatment consists of a surgical application of up to eight autologous, gene-corrected keratinocyte sheets for patients six years of age and older with recessive dystrophic epidermolysis bullosa (RDEB). The Phase III (VIITAL) trial studied two primary endpoints: wound healing and pain reduction. The first primary endpoint was the demonstration of ≥50% healing from baseline of RDEB wound size, which was met by the experimental group (81.4% vs. 16.3% control group). The study demonstrated a greater reduction in pain in the experimental group, which was the second co-primary endpoint. The treatment also was well-tolerated by patients. The costs for treatment will vary greatly, as it will depend on the size and number of open wounds to be treated.

Also in the pipeline is Castle Creek Bioscience's D-Fi/FCX-007 (dabocemagene autificel). Currently in Phase III clinical trials, D-Fi is a gene therapy constructed of autologously-derived COL7A1 gene corrected dermal fibroblasts (cells that contribute to the formation of connective tissues). Treatment is being administered to claimants two years of age and older with clinical diagnosis of RDEB with confirmation of COL7A1 genetic mutation.

Early phase trials showed minimal adverse effects and 80 percent target wound complete closure with treatment at week 12. Phase III studies will seek to confirm safety and efficacy of two or more treatment sessions (day 1, then week 12, followed by additional treatments if needed at weeks 24 and 36) with a 15-year follow-up. The primary outcome measure is complete wound closure of the first wound pair at week 24. There is no PDUFA date set for approval at this time, but it is anticipated for sometime in 2025. The costs for treatment will vary greatly as it will depend on the size and number of open wounds to be treated.

RHEACELL's stem cell therapy product allo-APZ2-OTS is currently in two Phase III clinical trials with anticipated approval no earlier than 2026. This treatment is considered an off-the-shelf (OTS) product manufactured from healthy human donor skin tissues. It is comprised of ABCB5-positive mesenchymal stem cells, which are thought to modulate inflammation. Treatment is administered as three IV infusions over 35 days, and it is unclear if repeat cycles will be needed. Costs for a one-time cycle are estimated with a WAC between $2,000,000 and $3,000,000.

Cost Containment Considerations

As part of its HMConnects™ cost containment program, HM Insurance Group (HM) works to support cost management opportunities around the use of gene and cell therapies and other high-cost pharmaceutical treatment options that can impact our clients' bottom line. The Pharmacy Operations (RxOps) team watches the market — and our book of business — to anticipate how current and future advancements will impact financial risk levels for HM's client base. Standard practices include reviewing, auditing and collaborating on the content of current policies, monitoring trends and implementing appropriate cost savings techniques. Additional practices include identifying the stockpiling of medications, determining if prescriptions are filled via in-network pharmacies and confirming that prescriptions are properly dosed based on weight and lab values when appropriate. All of these services are provided to HM's clients at no additional cost to them.

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Resources: [1]National Institute of Arthritis and Musculoskeletal and Skin Diseases, Epidermolysis Bullosa (September 2023), https://www.niams.nih.gov/health-topics/epidermolysis-bullosa#:~:text=Overview%20of%20Epidermolysis%20Bullosa,appear%20anywhere%20on%20the%20body, accessed April 3, 2024; [2]National Organization for Rare Disorders, Epidermolysis Bullosa (January 2024), https://rarediseases.org/rare-diseases/epidermolysis-bullosa/, accessed May 3, 2024; [3]Filsuvez (birch triterpenes) Topical Gel Package Insert, Wahlstedt, Germany: Lichtenheldt GmbH Pharmazeutische Fabrik Werk, December 2023; [4]Abeona Therpaeutics, Abeona Therapeutics Announces Positive Toplien Results with Both Co-Primary Endpoints Met in Pivotal Phase 3 VIITAL™ Study of EB-101 (November 2022), https://www.globenewswire.com/news-release/2022/11/03/2547492/0/en/Abeona-Therapeutics-Announces-Positive-Topline-Results-with-Both-Co-Primary-Endpoints-Met-in-Pivotal-Phase-3-VIITAL-Study-of-EB-101.html, accessed May 5, 2024; [5]Vyjuvek (beremagene geperpavec-svdt) package insert. Pittsburgh, PA: Krystal Biotech, Inc; 2023 May. [6]Phase 3, Open-label Clinical Trial of EB-101 for the Treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB) VIITAL: A Phase 3 Study of EB-101 for the Treatment of Recessive Dystrophic Epidermolysis Bullosa (RDEB), https://clinicaltrials.gov/study/NCT04227106?intr=NCT04227106&limit=10&rank=1, accessed May 2, 2024; [7]From Clinical Phenotype to Genotypic Modelling: Incidence and Prevalence of Recessive Dystrophic Epidermolysis Bullosa (RDEB) , National Library of Medicine, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6935313/#:~:text=To%20date%2C%20the%20widely%20estimated,of%20clinical%20databases%20or%20registries, accessed January 2024; [8]Epidermolysis Bullosa - Symptoms and Causes, Mayo Clinic, https://www.mayoclinic.org/diseases-conditions/epidermolysis-bullosa/symptoms-causes/syc-20361062, accessed January 2024; [9]A Study of FCX-007 for Recessive Dystrophic Epidermolysis Bullosa (DEFI-REDEB), A Pivotal Phase 3 Study of FCX-007 (Genetically-Modified Autologous Human Dermal Fibroblasts) for Recessive Dystrophic Epidermolysis Bullosa, https://clinicaltrials.gov/study/NCT04213261?intr=FCX-007&rank=1, accessed May 9, 2024; [10]Khan A, Riaz R, Ashraf S, Akilimali A. Revolutionary Breakthrough: FDA Approves Vyjuvek, the First Topical Gene Therapy for Dystrophic Epidermolysis Bullosa, Ann Med Surg (Lond), 2023;85(12):6298-6301; [11]Guide SV, Gonzalez ME, Bağcı IS, et al. Trial of Beremagene Geperpavec (B-VEC) for Dystrophic Epidermolysis Bullosa, N Engl J Med, 2022;387(24):2211-2219; [12]IPD Analytics, Epidermolysis Bullosa, RxInsights, Vyjuvek, https://secure.ipdanalytics.com/User/Pharma/RxStrategy/Page/378b4d5a-0740-4d04-ad34-fefdd7f903ab#section-group-553277, accessed January 2024.

MX3785634 (6/24)