

Guide for reducing the risks of medicinal products and their application
Healthcare Providers

Vyjuvek (beremagene geperpavec)

5×10⁹ plaque-forming units/mL suspension
and gel for gel

Please also refer to the prescribing information for Vyjuvek.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. HCPs are asked to report any suspected adverse events (see last page for information on how to report adverse events).

The pages of this guide are color-coded to make information easier to find:

Gray: General information

Blue: Information on preparing Vyjuvek

Green: Information on applying Vyjuvek

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What is Vyjuvek?

Vyjuvek (beremagene geperpavec) is indicated for the treatment of wounds in patients with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha-1 chain gene (*COL7A1*) from birth. Beremagene geperpavec is a replication-defective herpes simplex type 1 (HSV-1)-based gene therapy vector genetically engineered to express human type VII collagen protein (COL7) controlled by the Human Cytomegalovirus (hCMV) promoter.

Beremagene geperpavec is produced in Vero (monkey kidney) cells by means of recombinant DNA technology. It does not replicate in cells, interact with or integrate into native DNA.

Vyjuvek consists of a suspension and an excipient gel for the preparation of a gel.

Prior to use, the suspension and the excipient gel must be **thawed and mixed at a pharmacy**.

For information on preparing Vyjuvek, see the chapter "Preparing Vyjuvek for application".

Treatment with Vyjuvek must be initiated by healthcare professionals with experience in treating people with dystrophic epidermolysis bullosa and is **generally performed in medical facilities**. Whether **application in a home environment** by qualified medical personnel or the patient/a caregiver **after they have received proper training** is appropriate must be determined by the treating physician.

For information on applying Vyjuvek, see the chapter "Application of Vyjuvek".

Safety precautions

Please note:



Because this medicinal product contains genetically modified organisms, anyone preparing, administering or disposing of Vyjuvek (or assisting with these tasks) must wear **protective equipment** (e.g. gown, disposable gloves, mask and eye protection). **Avoid any direct, unprotected contact** with Vyjuvek.



If you are **pregnant**, you **must not come into contact with Vyjuvek**, or with skin or dressings that have come into contact with Vyjuvek. Do not prepare or apply Vyjuvek and do not assist anyone in doing so.

Measures to take after accidental contact with Vyjuvek



If Vyjuvek gets **into your eyes or on your mucous membranes** (e.g. nose, mouth), thoroughly rinse the affected area(s) **with clean water for at least 5 minutes**.



If your **skin** comes into contact with Vyjuvek or in the event of a needle prick injury, thoroughly **wash** the affected area with **soap and water and/or a virucidal disinfectant** (e.g. 70% isopropyl alcohol, 6% hydrogen peroxide or < 0.4% ammonium chloride).



If **surfaces** unintentionally come into contact with Vyjuvek, clean them using a **virucidal disinfectant**.

Preparing Vyjuvek for application

What to know before preparing Vyjuvek

- Each shelf carton contains



1 vial with suspension

(1 mL removable volume containing 5×10^9 PFUs)
(green cap)



1 vial with excipient gel

(1.5 mL)
(blue cap)

- Each vial with suspension contains 1 mL in removable volume of a suspension containing 5×10^9 plaque-forming units (PFU) of Vyjuvek.
- After mixing 1 mL of the suspension with the excipient gel, Vyjuvek contains 5×10^9 PFU in 2.5 mL.
- The removable volume is 2.0 mL (4×10^9 PFU) at a concentration of 2×10^9 PFU/mL.
- Preparation results in four 1 mL syringes, each filled with 0.5 mL Vyjuvek.
- If preparation was done under **clean room conditions** (laminar air flow), the 1 mL syringes can be stored for **7 days at a temperature of 2°C to 8°C**. **Otherwise**, the syringes may be stored at **2°C to 8°C for up to 24 hours**.
- After **removing the syringes from refrigeration**, Vyjuvek must be used **within 8 hours**.



Video „Preparing Vyjuvek” and demonstration kit

The Vyjuvek **reconstruction video** is available by flashing the QR code or on the website: <http://ema.krystallabel.com>.

You can request a **demonstration kit** with vials (without active ingredient) and syringes to practice reconstituting Vyjuvek. Order it from medinfo.estonia@swixxbiopharma.com

Preparation

Required materials



You will need:

- 1 Shelf carton containing Vyjuvek
(one vial of suspension and one vial of excipient gel)
- 2 One 3 mL syringe
- 3 Four 1 mL syringes with caps
- 4 Two needles (e.g. 16G or 18G)
- 5 Alcohol swabs
- 6 Protective equipment
(e.g. gown, disposable gloves, mask and eye protection)
- 7 Sealable plastic bag(s)

Step 1: Pre-Preparation



- Anyone preparing or assisting with the preparation of Vyjuvek must don the **protective equipment** prior to doing so.



- Remove the frozen vials from the shelf carton and let them **thaw** at room temperature (for about 30 minutes). Note that vials, once thawed, **may not be refrozen**.
- Inspect the **thawed suspension**: It may contain white or whitish particles. Its color may range from opalescent yellow to colorless. **Do not use the medicinal product** if you notice any discoloration outside this range.
- Inspect the **thawed excipient gel**: It should be clear, colorless, and viscous. **Do not use the excipient gel** if you notice any particles or discoloration.



- Carefully invert the vial containing the suspension 4-5 times to **mix its contents**.



- **Remove the protective caps** from both vials.



- **Clean the rubber stoppers** of both vials with alcohol swabs and allow them to dry.

Step 2: Transferring and mixing



- Hold the vial with the thawed suspension at an oblique angle (45 to 90 degrees) and use the **3 mL syringe** and a needle (e.g. 16G or 18G) to **remove 1 mL** of the suspension.



- **Transfer** this 1 mL of suspension into the vial containing the thawed gel and then **leave** the syringe inserted in this vial.
- Next, pull the syringe partially out of the vial so that the **tip of the needle is just above the liquid**.
- **Aspirate** 1 mL of **air** from the vial (air pocket) in order to equalize the pressure in the vial after adding the suspension.



- **Remove** the syringe (including the needle) and ensure its proper **disposal**.



- **Cover the stopper** of the vial with an **alcohol swab**.
- **Shake** the vial **vigorously** for at least **10 seconds**. This should yield a homogeneous gel inside the vial.
- **Inspect** the medicinal product in the vial for the following:
 - It may contain **white or whitish particles**.
 - Its color may range from **opalescent yellow to colorless**.

Do not use the medicinal product if you notice any discoloration outside this range.

Vyjuvek is now ready to use. We will refer to the vial containing the combination of suspension and gel as the Vyjuvek vial from here on.

Step 3: Drawing up the Vyjuvek syringes

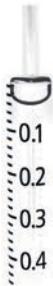
0.5 mL



- Take a **1 mL syringe** and attach a **fresh needle** (16G or 18G) to it.
- **Slowly draw 0.5 mL** of gel from the Vyjuvek vial into the syringe while holding the vial at an oblique angle (45 to 90 degrees).
- **Leave** the syringe in the Vyjuvek vial. Only pull the syringe partially out of the vial so that the **tip of the needle is just above the liquid**.



- Still keeping the needle inserted in the Vyjuvek vial, detach the **syringe from the needle**.
- A small **air pocket** may form, this is expected.
- **Invert the syringe** so the syringe tip is pointing upwards.
- If an **air pocket** has formed in the syringe, push the plunger into the syringe and pull it back again a few times until the air has been expelled. **DO NOT tap** the syringe to release the air!



Tiny air bubbles may remain in the syringe, this is expected.



- **Cap** the syringe and set it aside.

Now, fill the **next 1 mL syringe**.



- Attach a **new 1 mL syringe to the needle** (that is still inserted in the Vyjuvek vial).
- **Repeat step 3** "Drawing up the Vyjuvek syringes" until the desired number of syringes has been filled and capped.

The maximum removable volume is 2.0 mL (4×10^9 PFUs).

Step 4: Labeling Vyjuvek syringes



- **Label** the syringes with the following:
 - Patient ID
 - Vyjuvek (name of the medicinal product)
 - Batch number
 - “Use by” date
 - Storage conditions



Make sure **not to obscure** the grading on the syringes while labeling them.

Step 5: Packaging Vyjuvek syringes



- Place the Vyjuvek syringes in a sealable **plastic bag** to protect them from light and seal the bag.
- **Label** the plastic bag with the following:
 - Patient ID
 - Vyjuvek (name of the medicinal product)
 - Batch number
 - “Use by” date
 - Storage conditions
- Place the plastic bag with the Vyjuvek syringes in a **suitable insulated tertiary container (“outer container”)** that allows for them to be transported at a temperature of 2°C to 8°C and that protects the medicinal product against light.
- Enclose the **instructions for use** in the container.
- **Close** the outer container. It may only be opened again at the place of use.
- **Label** the outer container with the sender and recipient addresses.

Cleaning and disposal

Clean any **surfaces** that have come into contact with Vyjuvek using a **virucidal disinfectant** and dispose of any **unused medicinal product, vials, used syringes and needles, alcohol swabs and used cleaning material that has come into contact with Vyjuvek** in a sealable plastic bag. Continue to wear protective equipment while doing so.

Storage and transportation

Storage of unopened shelf cartons

- Store the vials in the **shelf cartons**.
- Store all unopened shelf cartons at **-15°C to -25°C** if possible (shelf life: 2 years).
- If storage **in a freezer is not possible**:
Store at **2°C to 8°C** (shelf life: up to a maximum of 1 month).
- Once thawed, vials **may not be refrozen**.

Storing Vyjuvek syringes

- Leave the syringes in the **outer container**.
- Store the syringes in a **clean place free of potential contamination** and **keep them away from children**.
- If preparation was done under **clean room conditions** (laminar air flow), the syringes can be stored for **7 days at a temperature of 2°C to 8°C**. **Otherwise**, the syringes may be stored at **2°C to 8°C for up to 24 hours**.
- After **removing the syringes from refrigeration**, Vyjuvek must be used **within 8 hours**.

Transporting Vyjuvek from the pharmacy

The Vyjuvek syringes must be transported at **2°C to 8°C** from the pharmacy to the place of use. Ensure that a suitable **outer container for refrigerated, light-protected transportation** is provided when picking up the product from the pharmacy.

Receiving the syringes at the clinic/office

If the pharmacy delivers or ships the syringes, these are delivered in an **outer container** that may only be opened by the person **responsible for applying Vyjuvek**. This person must also confirm the **integrity of the outer container** and that there are no signs of leaking. If any damage or leakage has occurred, please immediately notify your pharmacy.

Application of Vyjuvek



Please note:

- Treatment with Vyjuvek must be initiated by healthcare providers with experience in treating people with dystrophic epidermolysis bullosa.
- Because this medicinal product contains genetically modified organisms, anyone applying or disposing of Vyjuvek (or assisting with these tasks) must wear **protective equipment** (e.g. gown, disposable gloves, mask and eye protection).
- **If you are pregnant, you must not come into contact with Vyjuvek, or with skin or dressings that have come into contact with Vyjuvek. Do not apply Vyjuvek and do not assist anyone in doing so.**
- Apply Vyjuvek **once a week**.
- Use Vyjuvek **before the use-by date provided by the pharmacy**.
- **Do not apply** Vyjuvek to wounds with a confirmed or suspected diagnosis of **squamous cell carcinoma**.
- Vyjuvek has been tested for **sterility**. Nevertheless, a transmission of infectious agents cannot be completely ruled out. Monitor patients for any **signs of infection** after application. If necessary, initiate appropriate treatment.
- Treatment with Vyjuvek can be done as part of a **routine dressing change**.

Vyjuvek administration video and demo kit



The Vyjuvek administration video is available by flashing the QR code or on the website: <http://ema.krystallabel.com>.

You can request a **demonstration kit** with syringes (without active ingredient) to practice administering Vyjuvek and/or train the person who will perform the administration. Order it from the following address medinfo.estonia@swixxbiopharma.com

Step 1: Preparation

Step 1.1: Preparation of the work area



- Clean the work area with a **virucidal disinfectant** and set up the materials you will need:



- 1 **syringes** filled with Vyjuvek
- 2 a **hydrophobic** dressing slightly larger than the selected wound
- 3 a **standard wound dressing** (that is slightly larger than the water-repellent dressing)
- 4 a **pair of scissors**
- 5 **protective equipment** (e.g. gown, disposable gloves, mask and eye protection)
- 6 **wound cleanser** (**without** virucidal ingredients)
- 7 **disinfectant** (**with** virucidal ingredients)
- 8 a sealable **plastic bag** (for disposal)

Please **note** that you will need to use **two different cleaning/disinfecting products**:



For the wound:
a **wound cleanser**
WITHOUT virucidal ingredients



For surfaces and materials
that have been in contact with Vyjuvek:
a **disinfectant with** virucidal ingredients



- Anyone applying or assisting with the application of Vyjuvek must don the **protective equipment** prior to doing so.



- Inspect the medicinal product:
 - Do not use Vyjuvek after the **expiry date**.
 - The **color of the medicinal product** may range from opalescent yellow to colorless. **Do not use it** if you notice a discoloration outside this range.

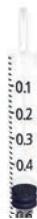
If this happens, notify your pharmacy.

Step 1.2: Preparing the selected wound

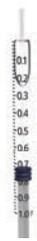


- **Carefully remove** dead skin, scabs and wound fluid as well as any medicinal products and ointments from the wound area and **gently cleanse** the wound using a **wound cleansing agent without virucidal ingredients**, e.g. sterile saline solution.

Step 1.3: Preparation of the syringe



- Hold the syringe with **its tip pointing upwards**.



- **Pull the plunger a little**, but not completely, out of the syringe.



- Now, **slowly push** the plunger **back into the syringe** until a small drop of Vyjuvek exits the syringe tip.

Step 2: Applying Vyjuvek



Note:

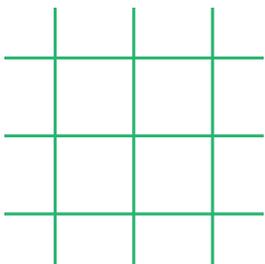
- Only apply Vyjuvek to the wound to be treated.
- Keep applying Vyjuvek to the same wound until it is **completely closed**. Only then start treating a new wound.
- If a previously treated wound **reopens**, continue by treating **this wound first**.
- **Do not apply any other medicines** to the wound at the same time as Vyjuvek.

The amount of Vyjuvek required may vary depending on the size of the wound. The table below shows **reference values for the dosage** based on wound size (in children, adolescents and adults).

Wound surface (cm ²)	Dose (PFU)	Volume (in mL)
<20	<4×10 ⁸	<0.2
20 to <40	4×10 ⁸ to <8×10 ⁸	0.2 to <0.4
40 to <60	8×10 ⁸ to <1.2×10 ⁹	0.4 to <0.6
60 to <200	1.2×10 ⁹ to <4×10 ⁹	0.6 to <2

Maximum dose per weekly application:

- Adults and children aged 3 years and over: 2 mL (4×10⁹ PFU)
- Children under 3 years of age: 1 mL (2×10⁹ PFU)



- Imagine a **grid with fields sized 1×1 cm** covering the selected wound (1 cm is roughly the width of the tip of your little finger).

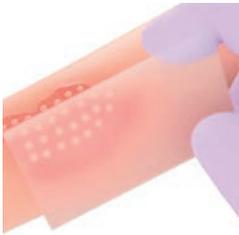


- Now, apply one drop of Vyjuvek **to each field of this imaginary grid.**



- Make sure that the tip of the syringe **does not touch the skin!**

Step 3: Bandaging the wound



- Cut the **water-repellent dressing** to a size **slightly larger than the treated wound** and place it on the wound in such a way that the edges of the dressing **fully extend beyond the wound surface area** on all sides.



- Afterwards, **completely cover** the above wound dressing with the patient's **standard dressing/bandage** (in order to prevent Vyjuvek from coming into contact with other areas of the skin).

Instruct your patients using the guide for patients and caregivers:

- that the Vyjuvek dressing must remain on the treated wound for **approx. 24 hours**,
- that the wound **should not be touched** during this time if possible,
- on the **first dressing change** after application (see Guide for Patients and Caregivers, section "The first dressing change after applying Vyjuvek"),
- on how to **dispose** of materials that have come into contact with Vyjuvek (see Guide for Patients and Caregivers, section "Cleaning and disposal"),
- on **what to do in the event of accidental exposure** to to Vyjuvek (see Guide for Patients and Caregivers, section "Measures to take after accidental contact with Vyjuvek").



Cleaning and disposal



- Clean any surfaces that have come into contact with Vyjuvek using a **virucidal disinfectant**.
- Disinfect everything that came or could have come into contact with Vyjuvek (e.g. dressings, used and unused syringes, used materials) **with a virucidal disinfectant**.



- Place these items in a **sealable plastic bag**. Seal and dispose of it with **household waste** or in accordance with local regulations.

Documentation



Clearly **document** the name of the medicinal product and the batch used to improve the traceability of biologics.

Applying Vyjuvek in a home environment

If deemed appropriate based on your medical expertise, Vyjuvek may also be applied in a **home environment** by qualified medical personnel, the patient and/or a caregiver after appropriate training.

Please **ensure** that the patient and/or the caregiver is able to do the following:

- adhere to hygiene requirements,
- apply Vyjuvek correctly and
- store and dispose of the product as per instructions.

Before Vyjuvek is first used in a home environment, the following steps are required:

- **Information and counseling** of the patient and/or caregiver on the use of Vyjuvek in a home environment by a healthcare provider.
- **Training of persons** who apply or assist in applying Vyjuvek **by a healthcare provider**. The **application** of Vyjuvek by patients/caregivers must be practiced under the supervision of a healthcare provider until the patient/caregiver has **fully mastered** the application process.
- Development of a personalized **treatment plan**.
 - This plan is to include **information on which wound(s) will be treated first** and which wound(s) will be treated after these are closed,
 - the **dosage** based on wound size and age of the patient,
 - a **schedule for follow-up appointments** at the office/clinic,
 - **instructions for monitoring/documenting** the treatment and
 - **contact information** for questions regarding the treatment or medication as well as for reporting adverse events.
- Provision and discussion of the **Guide for Patients and Caregivers**.



Vyjuvek may only be used in a home environment after all these conditions have been met!

Reporting adverse events

It is very important to report any suspected adverse events after market authorization. This enables the continuous monitoring of the risk-benefit ratio for the medicinal product.

Please report all adverse events to Estonian Health Authorities via www.ravimiamet.ee or to the local representative of the marketing authorisation holder Swixx Biopharma OÜ, via e-mail medinfo.estonia@swixxbiopharma.com.

Further information



All Vyjuvek training materials for healthcare professionals, patients and caregivers (guides for healthcare professionals, patients treated with Vyjuvek and their caregivers containing important safety information on the use of Vyjuvek, reconstitution video and Vyjuvek administration video) and all regulatory-approved drug information are also available online by flashing the QR code or at <http://ema.krystallabel.com>. Printed copies can be ordered via: medinfo.estonia@swixxbiopharma.com

REFERENCE: Vyjuvek, current package insert

