Guideline for the reduction ofdrug and application risks

Healthcare professionals

Vyjuvek (Beremagen geperpavec)

5×10^9 plaque-forming units/ml suspension and gel for the preparation of a gel

Please also refer to the Information for healthcare professionals on Vyjuvek

▼

This medicinal product is subject to additional monitoring. This enables rapid identification of new safety findings. Healthcare professionals are requested to report any suspected adverse reactions (see last page for information on reporting adverse reactions).

Status of the authorisation: [month][year] Version: 1.0 Job number

The coloured markings in the margins of this guide provide better orientation:

Grey: General information Blue:

Preparation information Green:

Application information

Contents

What is Vyjuvek?

Vyjuvek (beremagen geperpavec) is used for the treatment of wounds from birth in patients with dystrophic epidermolysis bullosa (DEB) with mutation(s) in the gene for the alpha-1 chain of collagen type VII (*COL7A1*). Beremagen geperpavec is a replication-defective herpes simplex type 1 (HSV-1)-based gene therapy vector genetically to express the human type VII collagen protein (COL7) under the control of the human cytomegalovirus (hCMV) promoter.

Beremagen geperpavec is produced in Vero cells (monkey kidney cells) using recombinant DNA technology. It does not replicate in cells, does not integrate into the native DNA and does not interact with it.

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

Before use, the suspension and the excipient gel must be **thawed and mixed in a pharmacy.**

Information on preparation can be found in the chapter "Preparation of the Vyjuvek dose".

Treatment with Vyjuvek is initiated by healthcare professionals with experience in the treatment of people with dystrophic epidermolysis bullosa and is **usually carried out in a medical setting.** It is up to the doctor to decide whether it can be **used at home** by healthcare professionals or by the patient or a carer **after training.**

Information on the application can be found in the chapter "Application of Vyjuvek".

Patients using Vyjuvek are recommended to participate in a non-inter-
The company will also participate in the international, cross-national **study on the long-term safety of** the drug (PASS-01).

Please inform your patients and/or their carers about this and ask them to take part in the study.

Precautionary measures

Please note

As this medicinal product contains genetically modified organisms, people who prepare, apply, dispose of or assist with Vyjuvek must wear **protective equipment** (e.g. gown, disposable gloves, mask and eye protection). **Avoid direct contact** with Vyjuvek.

If you are **pregnant, you must not come into contact with Vyjuvek** - not even with skin or dressings that have come into contact with Vyjuvek. Do not prepare, apply or assist in the application of Vyjuvek.

Measures to be taken in the event of accidental exposure to Vyjuvek

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

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

If **surfaces** have accidentally come into contact with Vyjuvek, clean them with a **disinfectant** (**with** virucidal agents).

Preparation of the Vyjuvek dose

Video "Preparation of the Vyjuvek dose" and demo kit

A **video on how** to **prepare** Vyjuvek is available by scanning the QR code or via http://ema.krystallabel.com.

You can request a **demo kit** with vials (without active pharmaceutical ingredients) to practise preparing Vyjuvek. Order it at:

Genesis Pharma
E-mail: medinfo@genesispharmagroup.com

Information before preparation

- Each folding box contains

1 vial with suspension

(1 ml removable volume with 5×10^9 PFU)
(green cap)

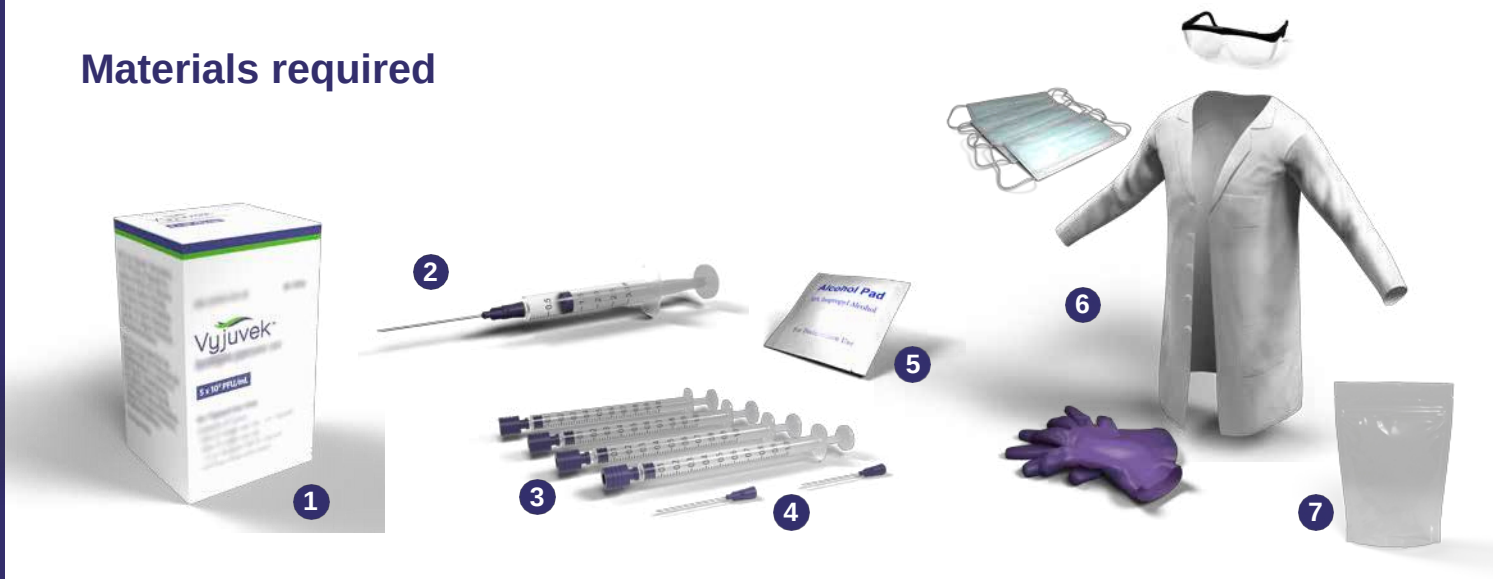
1 vial with excipient gel

(1.5 ml)
(blue cap)

- Each vial of suspension contains 1 ml withdrawable volume of 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 volume that can be removed is 2.0 ml (4×10^9 PFU), with a concentration of 2×10^9 PFU/ml.
- After preparation, four 1 ml syringes are obtained, each filled with 0.5 ml Vyjuvek.
- If the preparation was carried out **under clean room conditions** (*laminar air flow*), the 1 ml syringes can be stored **at 2 to 8 °C for 7 days. Otherwise,** the syringes can be stored **at 2 to 8 °C for 24 hours.**
- After **removing the syringes from the cooler**, Vyjuvek must be used **within 8 hours**. can be used.

Preparation

Materials required



You need

1. Folding box with Vyjuvek
   (one vial with suspension and one vial with excipient gel)
2. One 3 ml syringe
3. Four 1 ml syringes with caps
4. 2 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: **Preparation**

- Persons preparing or assisting in the preparation of vyjuvek should wear **protective equipment.**

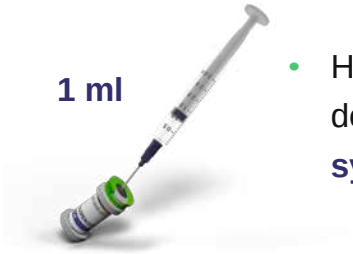
- Remove the frozen vials from the folding box and allow them to **thaw** at room temperature (this takes approx. 30 minutes).
  Please note that once thawed, vials must **not be refrozen**.
- Check the **thawed suspension:** it may contain white to whitish particulate matter. The colour may vary from opalescent yellow to colourless. **Do not use the medicine** if you notice any discolouration.
- Check the **thawed excipient gel:** it is clear, colourless and viscous. **Do not use the excipient gel** if you notice particulate matter or discolouration.

- Gently invert the vial of suspension 4 to 5 times **to mix** the **contents.**

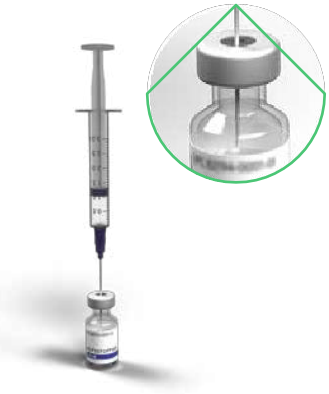
- **Remove the protective caps** from both vials**.**

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

Step 2: **Transfer and mix**



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



- **Transfer** this 1 ml into the vial with the thawed gel and then **leave** the syringe in this vial.
- Now pull the syringe out of the vial just enough so that the **needle tip is just above the liquid**.
- **Draw** 1 ml **of air** from the vial (air pocket) to equalise the pressure after addition.
- Then **remove** the syringe (incl. needle) and **dispose** of it properly.

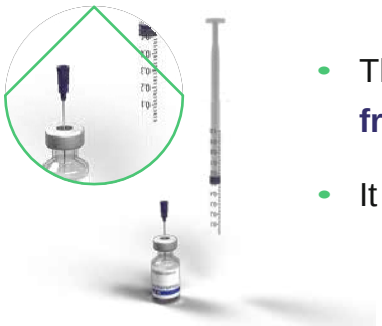
- **Cover the stopper** of the vial with a **Alcohol swabs.**
- **Shake** the vial **vigorously** for at least **10 seconds** long. A homogeneous gel should form.
- Check the medicine in the vial for the following:
  - It may contain **white to whitish particulate matter**.
  - The colour can vary from **opalescent yellow to colourless**.

  Do not use the medicine if you notice any discolouration.

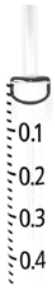
Vyjuvek is now mixed. The vial containing the combination of suspension and gel is referred to below as the Vyjuvek vial.

Step 3: **Drawing up the Vyjuvek syringes**

- Take a **1 ml syringe** and insert a **new needle** (16G or 18G).
- **Slowly draw 0.5 ml** from the Vyjuvek vial into the syringe. Hold the vial at an oblique angle (45 to 90 degrees).
- **Leave** the syringe in the Vyjuvek vial. Only pull the syringe out of the vial until the **needle tip is just above the liquid**.



- The needle remains in the Vyjuvek vial. Detach the **syringe from the needle.**
- It is normal for a small **air pocket** to form.



- **Turn the syringe over** so that the syringe tip is pointing upwards.
- If there is an **air pocket** in the syringe, push the syringe plunger into the syringe a few times and pull it back again until the air pocket has escaped. But **do not tap** the syringe to do this!
  It is normal for **small air bubbles** to remain in the syringe.

- Place **the sealing cap** on the syringe and set it aside.

The **next 1 ml syringe** is now **filled.**

- Place a **new 1 ml syringe on the needle** (which is still in the Vyjuvek vial).
- **Repeat step 3** "Drawing up the syringes" until the desired number of syringes has been filled and sealed.

The removable volume is 2.0 ml (4×10^9 PFU).

Step 4: **Labelling the Vyjuvek syringes**

- **Label** the syringes as follows:
  - Patient ID
  - Vyjuvek (name of the medicinal product)
  - Batch number
  - Date "usable until"
  - Storage conditions

Make sure that the syringe markings required for the application are **not covered**.

Step 5: **Packing the Vyjuvek syringes**

- Place the Vyjuvek syringes in a sealable **plastic bag,** to protect them from light, and close it.
- **Label** the plastic bag as follows:
  - Patient ID
  - Vyjuvek (name of the medicinal product)
  - Batch number
  - Date "usable until"
  - Storage conditions
- Place the plastic bag with the Vyjuvek syringes in **a suitable insulated tertiary container ("outer container"),** which ensures transport at 2 to 8 °C and protects the medicine from light.
- Please enclose the **instructions for use** with the container.
- Now **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 **surfaces** that have come into contact with Vyjuvek with a **disinfectant** (**with** virucidal agents) and dispose of **unused medication, vials, used syringes and needles, alcohol swabs and used cleaning materials that** have **come into contact with Vyjuvek**. Continue to wear protective equipment.

Storage and transport

Storage of unopened folding boxes

- Store the vials in the **folding box**.
- If possible, store unopened folding boxes **at -15 to -25 °C** (shelf life: 2 years).
- If storage in the **freezer is not possible**: Store at **2 to 8 °C** **(**shelf life: max. 1 month).
- Once thawed, vials must **not refrozen**.

Storage of the Vyjuvek syringes

- Leave the syringes in the **outer container.**
- Store the syringes **in a clean** place that is **inaccessible to children** and **free from potential contamination.**
- If the preparation was carried out **under clean room conditions** (*laminar air flow*), the syringes can be stored **at 2 to 8 °C** for **7 days**. **Otherwise,** the syringes can be stored **at 2 to 8 °C for 24 hours.**
- After **removing the syringes from the cooler**, Vyjuvek must be used **within 8 hours**. can be used.

Transport from the pharmacy

The Vyjuvek syringes must be transported at **2 to 8 °C** from the pharmacy to the place of use. When collecting from the pharmacy, ensure that a suitable **outer container** provided **for refrigerated and light-protected transport**.

Receipt of syringes in clinic/practice

When the pharmacy delivers or sends the syringes, they are delivered in an **outer container** that may only be opened by the person **responsible for** the **application**. This person must also ensure that the **outer container** is **intact** and shows no signs of leakage. In this case, please inform the pharmacy immediately.

Application of Vyjuvek

Video "Application from Vyjuvek" and demo kit

A **video on the preparation and application** of Vyjuvek is available by scanning the QR code or via http://ema.krystallabel.com/.

You can request a **demo kit** with syringes (without active pharmaceutical ingredients) to demonstrate the application of Vyjuvek and/or to train the person applying Vyjuvek. Order it at:

Genesis Pharma
E-mail: medinfo@genesispharmagroup.com

Please :

- Treatment with Vyjuvek should be initiated by healthcare professionals who have experience in treating people with dystrophic epidermolysis bullosa.
- As this medicinal product contains genetically modified organisms, persons applying, disposing of or assisting in the application of Vyjuvek must **wear protective equipment** (e.. gown, disposable gloves, mask and eye protection).
- If you are **pregnant, you must not come into contact with Vyjuvek** - not even with skin or dressings that have come into contact with Vyjuvek. Do not apply Vyjuvek and do not assist in doing so.
- Vyjuvek **once a week**.
- Vyjuvek within the **period specified 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, the transmission of infectious agents cannot completely ruled out. Monitor patients for **signs of infection** after use and initiate appropriate treatment if necessary.
- Treatment with Vyjuvek can be carried out as part of a **routine dressing change.**

Step 1: **Preparation**

Step 1.1: **Preparing the work area**

- **Clean** the work area with a **disinfectant** (**with** virucidal agents) and provide the necessary materials:

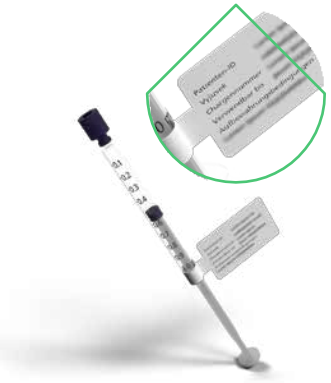
1. **Syringes** filled with Vyjuvek
2. **Hydrophobic** dressing (which is slightly larger than the selected wound)
3. **Standard dressing** (which is slightly larger than the hydrophobic
4. dressing) **Scissors**
5. **Protective equipment** (e.g. gown, disposable gloves, mask and eye protection)
6. **Wound cleanser** (**without** virucidal active ingredients)
7. **Disinfectant** (**with** virucidal active ingredients) Sealable
8. **plastic bag** (for disposal)

note that you need to use **two different cleaning/disinfectant agents.**
need:

For the wound: wound cleanser without
virucidal active ingredients

For surfaces and materials that have been in contact with Vyjuvek:
Disinfectant with virucidal active ingredients

- Persons applying or assisting with the application of Vyjuvek should wear **protective equipment.**



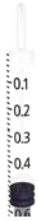
- Check the medicine:
  - Do not use it after the **expiry date.**
  - **The colour of the medicine** can vary from opalescent yellow to colourless. **Do not use it** if you notice any discolouration.

  Inform your pharmacy in these cases.

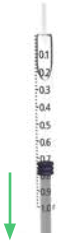
Step 1.2: **Preparation of the selected wound**

- Carefully **remove** dead skin, scabs and wound fluid as well as all medications and ointments from the wound area and gently clean the wound with a **wound cleanser (without** virucidal agents, e.g. sterile NaCl solution).

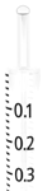
Step 1.3: **Preparing the syringe**



- Hold the syringe so that the **syringe tip** is **pointing upwards**.



- **Pull the syringe plunger** back slightly (but not completely out of the syringe).



- Then **slowly push** the syringe plunger **back into the syringe** until a small drop of Vyjuvek emerges from the syringe tip.

Step 2: **Applying Vyjuvek**

Please note:

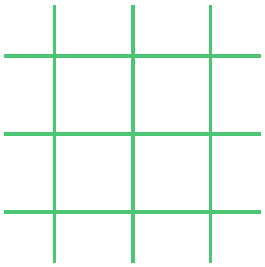
- **Only** apply Vyjuvek **to the wound to be treated.**
- Apply Vyjuvek to a wound until it is **completely closed**. Only then treat a new wound.
- If a wound that has already been treated **reopens, continue to** treat it **first.**
- **Do not any other medicines** to the wound **at the same time** 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** depending on the size of the wound area (in children, adolescents and adults).

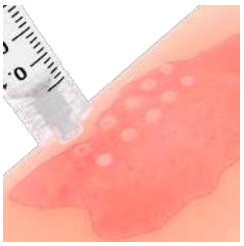
Wound area (cm^2)	Dose (PFU)	Volume (in ml)
< 20	$< 4\times10^8$	< 0,2
20 to< 40	4×10^8 to $< 8\times10^8$	0.2 to< 0.4
40 to< 60	8×10^8 to $< 1.2\times10^9$	0.4 to< 0.6
60 to< 200	1.2×10^9 to $< 4\times10^9$	0.6 to< 2

Maximum dose per weekly application:

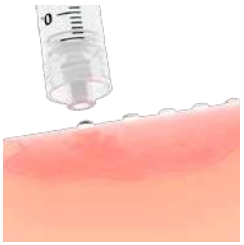
- Adults and children from 3 years: 2 ml (4×10^9 PFU)
- Children under 3 years: 1 ml (2×10^9 PFU)



- Imagine **a grid with 1× 1 cm squares** placed on the selected wound (1 cm is approximately the width of a fingertip).

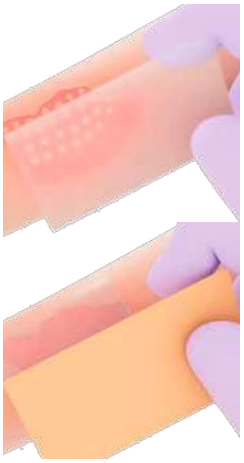


- Now apply **a drop to each of these (imaginary) fields** Vyjuvek.



- The syringe tip must **not touch** the skin**!**

Step 3: **Dressing the wound**



- Cut the **hydrophobic dressing** so that it is **slightly larger than the treated wound** and place it on the wound so that the edges of the dressing are **outside the wound area** everywhere**.**

- Then **cover** the above dressing completely **with the standard dressing** (to prevent Vyjuvek from being transferred to other areas).

Train your patients using the guidelines for patients and carers

- that the Vyjuvek dressing should remain **on the wound for about 24 hours**,
- that the wound should **not** be **touched** during this time if possible,
- for the **first dressing change** after application (see guidelines for patients and carers, section "The first dressing change after using Vyjuvek"),
- for the **disposal of** materials that have come into contact with Vyjuvek (see the "Cleaning and disposal" section of the guidelines for patients and carers),
- on **what** to **do in the event of accidental exposure to** Vyjuvek (see the "Measures to be taken in the event of accidental contact with Vyjuvek" section of the guidelines for patients and carers).

Cleaning and disposal

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

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

Documentation

Clearly **document** the name of the medicinal product and the batch to improve the traceability of biological medicinal products.

Use of Vyjuvek in the home environment

According to your professional judgement, Vyjuvek can also be used in **the home environment** by healthcare professionals, the patient and/or a carer after training.

Please ensure that the patient and/or carer is able do so**,**

- comply with the hygiene requirements,
- Vyjuvek correctly,
- Vyjuvek must be stored and disposed of in accordance with the instructions.

The following steps are necessary **before the first application in the home environment**:

- **Medical education and counselling** of patient and (if applicable) carer on the use of Vyjuvek in the home environment
- **Medical training of persons** who apply or support the application of Vyjuvek. **The application of** Vyjuvek by the patient/carer must be practised under medical supervision until the person **has mastered** it **safely.**
- Creation of an individual **treatment plan** including
  - **Determine which wound(s)** will be treated **first** and which will be treated after closure of the initially treated wound(s),
  - **Dosage** based on wound size and age of the ,
  - **Determination of follow-up appointments** at the practice/clinic,
  - **Specifications for monitoring/documenting** the course of therapy,
  - **Contact options** for questions about therapy or medication and for reporting side effects.
- Handing out and discussing the **guidelines for patients and carers**

Vyjuvek is only allowed to stay at home after these steps have been taken. be applied!

Reporting of side effects

The reporting of suspected adverse reactions after authorisation is of great importance. It enables continuous monitoring of the risk-benefit ratio of the medicinal product. Healthcare professionals are requested to report suspected adverse reaction to the Paul-Ehrlich-Institut or Krystal Biotech.

Bulgarian Drug Agency (BDA)
8 Damyan Gruev Str.,
Sofia 1303, BULGARIA
phone: +359 2 8903 417
fax: +359 2 8903 434 e-mail: bda@bda.bg

www.bda.bg/ Form for reporting adverse drug reactions by non-medical persons

or

GENESIS Pharma Bulgaria EOOD
Interpred- World Trade Center
Dragan Tsankov Blvd., Floor 7, Office 702
Sofia 1040
Tel: +359 2 969 3227
Email: Safety.Bulgaria@genesispharmagroup.com

Further information

All Vyjuvek training materials for healthcare professionals and for patients and carers (safe use guide, preparation video, application video) and all officially approved product information are also available online by scanning the QR code or via http://ema.krystallabel.com. Printed copies can ordered from Krystal Biotech (see contact details above).

REFERENCE: Vyjuvek, current technical information.

GENESIS Pharma Bulgaria EOOD
Interpred- World Trade Center
Dragan Tsankov Blvd., Floor 7, Office 702
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