ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Vyjuvek 5×10^9 plaque forming units/mL suspension and gel for gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Beremagene geperpavec is a replication-defective Herpes Simplex Type-1 HSV-1-based gene therapy vector that has been genetically modified to express the human type VII collagen (COL7) protein under the control of the human cytomegalovirus (hCMV) promoter.

Beremagene geperpavec is produced in Vero cells by recombinant DNA technology.

2.2 Qualitative and quantitative composition

Each vial contains 1 mL extractable volume of suspension containing 5×10^9 plaque forming units (PFU) of beremagene geperpavec.

After mixing 1 mL of the suspension with the gel, Vyjuvek contains 5×10^9 PFU in 2.5 mL. Extractable volume is 2.0 mL (4×10^9 PFU).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Suspension and gel for gel.

The suspension is opalescent yellow to colourless following thaw from its frozen state.

The gel is a clear viscous gel following thaw from its frozen state.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vyjuvek 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 (COL7A1)* gene, from birth.

4.2 Posology and method of administration

Vyjuvek should be initiated by healthcare professionals experienced in the management of patients with dystrophic epidermolysis bullosa.

Posology

Vyjuvek is applied cutaneously to wound(s) once a week in small droplets in a grid-like pattern, approximately 1-cm by 1-cm apart. All wounds may not be possible to be treated at each treatment visit.

The recommended total maximum weekly dosing for children from birth up to 3 years old is 1 mL (2×10^9 PFU). The recommended total maximum weekly dosing for children above 3 years of age, adolescents, and adults is 2 mL (4×10^9 PFU).

Vyjuvek should be applied to wounds until they are closed before selecting new wound(s) to treat. Weekly treatment of previously treated wounds should be prioritised if they re-open. If no wounds are present, Vyjuvek should not be administered.

The table below provides a reference on dose per approximate size of the wound in children, adolescents, and adults.

Table 1. Dose by wound area

Wound area (cm^2)*	**Dose (PFU)[a]**	**Volume (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

PFU= plaque forming units.
a: The maximum dose in children below 3 years of age is 1 mL (2×10^9 PFU)

If a dose is missed, Vyjuvek should be administered as soon as possible, and weekly dosing should be resumed thereafter.

Special populations

Elderly population
No dose adjustment is required in patients ≥ 65 years old.

Method of administration

Precaution to be taken before manipulating or administering the product
This medicine contains genetically modified organisms (see section 4.4). During preparation, administration, and disposal, appropriate precautions must be taken. Personal protective equipment (e.g., gloves, mask, and eye protection) should be worn when handling Vyjuvek.

Pregnant women should not prepare or administer Vyjuvek and should avoid direct contact with the treated wounds, or dressings from the treated wounds (see section 6.6).

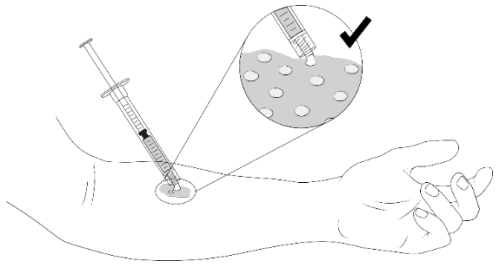
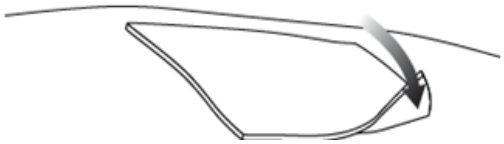
Administration
For cutaneous use on wounds only.

Prior to cutaneous use the suspension and gel must be thawed, and the suspension must be mixed into the gel in a pharmacy setting. For detailed instructions on preparation, shelf life after mixing, administration, measures to take in case of accidental exposure, logistics, and disposal of Vyjuvek, see sections 6.3 and 6.6.

A health care professional (HCP) should apply Vyjuvek, either at a healthcare professional setting (e.g., clinic) or the home setting. If deemed appropriate by the healthcare professional, trained patients or caregivers may also apply Vyjuvek.

Wounds should be gently cleaned prior to cutaneous administration using a product that does not contain a virucidal agent. Medicinal products and ointments at the wound area should be removed and the wound should be cleansed prior to Vyjuvek administration to ensure no reduction in its activity (see section 4.5).

Table 2. **Steps for administration**

Step 1. The Vyjuvek syringe should be primed prior to the initial application by pulling the plunger down and pushing it upwards, so that a small droplet of Vyjuvek forms at the tip of the syringe.	
Step 2. Vyjuvek should be applied to the selected wound, in small droplets approximately 1-cm by 1-cm apart (width of a fingertip) with only the droplet touching the wound. Only the gel should contact the skin. The tip of the syringe should not touch the skin to prevent the contamination of the gel in the syringe.	
Step 3. Once Vyjuvek has been administered to the wound, a hydrophobic dressing should be applied. The dressing should be cut to a size slightly larger than the wound but may vary upon patient preference. Once the Vyjuvek droplets are covered by the hydrophobic dressing, a thin even layer of Vyjuvek will form within the wound.	
Step 4. The standard dressing should be cut to a size larger than the hydrophobic dressing. The standard dressing will be placed over the hydrophobic dressing to prevent dissemination of the gel to other areas of the body or close contacts.	

The dressing should be left in place for approximately 24 hours after Vyjuvek application. Once the Vyjuvek dressings are removed, the patient may continue with their standard of care.

Vyjuvek should continue to be administered weekly until the wounds are closed. If previously treated wounds re-open, Vyjuvek should be applied again. If no wounds are present, Vyjuvek should not be administered.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of the biological medicinal product, the name and the batch number of the administered medicinal product should be clearly recorded.

Squamous cell carcinoma

Vyjuvek should not be applied to wounds with a confirmed or suspicious diagnosis of squamous cell carcinoma (SCC). Vyjuvek may still be applied to other wounds in patients who develop SCC.

Transmission of an infectious agent

Beremagene geperpavec will not replicate in cells and does not integrate into or otherwise interact with the native DNA.

Although beremagene geperpavec is tested for sterility, a risk of transmission of infectious agents exists. Healthcare professionals administering Vyjuvek must, therefore, monitor patients for signs and symptoms of infections after treatment and treat appropriately, if needed.

Individuals handling beremagene geperpavec or assisting with dressing changes should wear protective equipment (see section 6.6).

Pregnant women should not handle dressing waste. Carers or HCPs applying the gel should comply with the requirement to cover wounds with dressings. Patients should also be advised to avoid touching or scratching wound sites to avoid contamination of other areas of the body or close contacts.

Long-term follow-up

Patients are expected to enroll in a non-interventional multi-country study, to assess the long-term safety of beremagene geperpavec in a real-life setting.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been conducted with Vyjuvek. Interactions with topical medicinal products have not been investigated in clinical trials. Other topical medicinal products should not be concomitantly administered with Vyjuvek.

The safety of immunisation with live viral vaccines during or following Vyjuvek treatment has not been studied. There is no data to suggest that Vyjuvek may interfere with the body's ability to appropriately respond to a live virus vaccines.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of beremagene geperpavec in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

The use of Vyjuvek is not recommended during pregnancy.

Breast-feeding

It is unknown whether beremagene geperpavec is excreted in human milk.

A risk to the newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Vyjuvek therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

No nonclinical or clinical studies have been performed to evaluate the effect of beremagene geperpavec on fertility.

4.7 Effects on ability to drive and use machines

Vyjuvek has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Eighteen patients (58%) in the clinical trial reported at least one adverse reaction. The most commonly reported adverse reactions were chills (9.7%) and pruritus (9.7%)..

No adverse reactions led to discontinuation.

Tabulated list of adverse reactions

Unless otherwise stated, the frequencies of adverse reactions are based on all causal adverse event frequencies identified in 31 patients exposed to beremagene geperpavec during a median duration of 25 weeks in the Phase 3 randomised, intra-subject placebo-controlled study. See section 5.1 for information on the main characteristics of patients in clinical trial.

In the following table, adverse reactions are listed by MedDRA system organ class (SOC), preferred term, and by frequency. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions is defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000), not known (cannot be estimated from the available data).

Table 3. Adverse reactions

System organ class **Preferred term**	**All subjects** **(N=31)**
Respiratory, thoracic and mediastinal disorders	
Cough	Common
Rhinorrhea	Common
Skin and subcutaneous tissue disorders	
Pruritus	Common
Erythema	Common
Rash	Common
General disorders and administration site conditions	
Chills	Common

Paediatric population

Of the 31 subjects in the Phase 3 study, 19 (61%) were paediatric subjects (17 years of age or less), including 3 (9.7%) aged 3 years or less. Of the 19 paediatric subjects, 8 were female (42%).

Given the identity of the product, and its route of administration and localized containment, frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Immunogenicity

There was minimal evidence of systemic vector exposure after cutaneous application of Vyjuvek. Antibodies against the viral vector (HSV-1) and transgene protein (COL7) were evaluated in a subset of subjects in the randomised, intra-subject placebo-controlled clinical study. A total of 64% of evaluated subjects (14/22) were anti-HSV-1 antibody positive at baseline. Six of the 8 anti-HSV-1 seronegative subjects seroconverted by week 26 following treatment with Vyjuvek. For subjects with available matched baseline and end-of-study serum samples, anti-drug antibodies (ADAs) to COL7 were detected in 72% (13/18) of subjects treated with Vyjuvek for up to 26 weeks. Neutralizing immunity was not observed at first or repeated Vyjuvek exposure. The impact of seroconversion on maintenance of treatment effect is unknown as data are not available after 26 weeks.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose of Vyjuvek has been reported. Symptomatic and supportive treatment, as deemed necessary by the treating healthcare professional, is advised in case of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Preparations for the treatment of wounds and ulcers, cicatrizants, ATC code: D03AX16

Mechanism of action

Beremagene geperpavec is a gene therapy based on an engineered, replication-defective herpes simplex virus 1 (HSV-1) encoded with COL7A1 gene, addressing the underlying genetic cause of dystrophic epidermolysis bullosa. The HSV-1 vector belongs to the human herpes virus (HHV) family of double-stranded DNA viruses. Upon cutaneous application to the wounds, beremagene geperpavec can transduce both keratinocytes and fibroblasts. Following entry of beremagene geperpavec into the cells, the vector genome is deposited in the nucleus without integrating into, or otherwise disrupting, host cell DNA. Once in the nucleus, transcription of the encoded human *COL7A1* is initiated. The resulting transcripts allow for production and secretion of COL7 by the cell in its mature form. These COL7 molecules arrange themselves into long, thin bundles that form anchoring fibrils. The anchoring fibrils hold the epidermis and dermis together and are essential for maintaining the integrity of the skin.

Clinical efficacy and safety

The efficacy of Vyjuvek in subjects one year of age and older with DEB with mutation(s) in the *COL7A1* gene was evaluated in a randomised controlled trial. All study subjects had DEB with genetically confirmed mutation(s) in the *COL7A1* gene. Two comparable wounds in each subject were selected and randomised to receive either cutaneous application of beremagene geperpavec or placebo (gel only) weekly for 26 weeks. The total maximum weekly dose was defined based on age category: subjects ≥ 6 months to < 3 years received 1.6×10^9 PFU/week, subjects ≥ 3 years to < 6 years received 2.4×10^9 PFU/week, and subjects ≥ 6 years received 3.2×10^9 PFU/week.

The study enrolled 31 subjects (20 males and 11 females), including 30 subjects with autosomal recessive DEB and one subject with autosomal dominant DEB. The size of the beremagene geperpavec-treated primary wounds ranged from 2 to 57 cm^2, with 74% of wounds < 20 cm^2 and 19% from 20 to < 40 cm^2. The size of the placebo gel-treated wounds ranged from 2 to 52 cm^2, with 71% of wounds < 20 cm^2 and 26% from 20 to < 40 cm^2. The largest size secondary wound treated was ≥ 130 cm^2. The mean age of the subjects was 17 years (1 year to 44 years), including 61% paediatric subjects (n=19, age 1 to < 17 years) and 9.7% subjects less than 3 years. Sixty-four percent of subjects were White; 19% were Asian, and the remainder were American Indian or Alaska Native.

Efficacy was assessed on the basis of improved wound healing defined as the difference in the proportion of complete (100%) wound closure at 24 weeks confirmed at two consecutive study visits 2 weeks apart, assessed at weeks 22 and 24 or at weeks 24 and 26, between the beremagene geperpavec -treated and the placebo gel-treated wounds. Efficacy was also assessed by the difference in the proportion of complete wound closure assessed at weeks 8 and 10 or at both weeks 10 and 12 between the beremagene geperpavec-treated and the placebo gel-treated wounds. Complete wound healing was defined as 100% wound closure from the exact wound area selected at baseline, specified as skin re-epithelialization without drainage, evaluated at two consecutive visits two weeks apart. The efficacy results are summarised in Table 4.

Table 4. Primary end point and key secondary end point*

Wound closure assessment timepoints	Primary wounds exposed to beremagene geperpavec (N=31)	Primary wounds exposed to placebo (N=31)	Absolute difference (95% CI)	p value
Primary end point: complete wound healing at 6 months†‡	20.9 (67%)	6.7 (22%)	46 (24-68%)	0.002
Key secondary end point: complete wound healing at 3months‡	21.9 (71%)	6.1 (20%)	51 (29-73%)	<0.001

*The primary and key secondary end points were analysed in the intention-to-treat population. Multiple-imputation methods were used to account for missing data. Fractional counts are due to the multiple-imputation procedure used for analysis. Hypothesis testing was performed with the use of exact McNemar's test.

†Primary wounds were assessed at weeks 22 and 24 or weeks 24 and 26.

‡Primary wounds were assessed at weeks 8 and 10 or weeks 10 and 12.

5.2 Pharmacokinetic properties

In the confirmatory trial, systemic exposure assessments were conducted at weekly clinical site visits via quantification of beremagene geperpavec genomes in blood and urine samples (vector shedding) using a validated qPCR assay. All blood samples and all but one urine sample collected throughout the study were below the limit of detection/quantification for all subjects, indicating no significant systemic exposure of the subjects to the vector.

Clinical pharmacokinetics and shedding

Biodistribution and vector shedding studies were supportive and indicated a lack of systemic exposure after localised, cutaneous administration of beremagene geperpavec.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of single and repeated dose administration in toxicology studies.

Animal developmental and reproductive toxicity studies have not been conducted.

No studies have been conducted to evaluate the effects of beremagene geperpavec on carcinogenesis, mutagenesis, or impairment of fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Suspension

Glycerol (E422)
Sodium chloride
Disodium phosphate (E339)
Potassium chloride (E508)
Dipotassium phosphate (E340)

Gel

Hypromellose (E464)
Trometamol
Sodium chloride
Disodium phosphate (E339)
Dipotassium phosphate (E340)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened cartons

2 years when stored in the freezer.

After thawing

If a freezer is not available, the carton(s) may be stored in a refrigerator (2°C to 8°C) for up to 1 month.

Once stored in the refrigerator, the medicinal product should not be re-frozen.

After mixing

Chemical and physical in-use stability has been demonstrated for 168 hours (7 days) at 2-8°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless mixing has taken place in controlled and validated aseptic conditions.

Syringes can be stored at room temperature for up to 8 hours.

Transport conditions for mixed product

Transport mixed product at 2-8°C to site of administration.

6.4 Special precautions for storage

Unopened cartons

Store frozen at -15°C to -25°C. Transport frozen (< -20°C).

Keep the vials in the carton prior to thawing in order to protect from light.

After thawing and mixing

For storage conditions after thawing and after mixing of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each carton of Vyjuvek contains one vial of suspension and one vial of gel.

Suspension

1 mL extractable volume containing 5×10^9 PFU in a cyclo-olefin copolymer vial with a thermoplastic elastomer closure and green cap.

Gel

1.5 mL fill volume in a separate Type-1 glass vial with a bromobutyl elastomer stopper and blue cap.

6.6 Special precautions for disposal and other handling

Precautions to be taken before handling or administering the medicinal product

This medicine contains genetically modified organisms (see section 4.4). During preparation, administration, and disposal, appropriate precautions must be taken. Personal protective equipment (e.g., gloves, mask, and eye protection) should be worn when handling Vyjuvek.

HCPs or carers who are pregnant should not administer Vyjuvek and should not come into direct contact with treated wounds, or all material that has been in contact with treated wounds.

Preparation prior to administration

Follow the steps below for Vyjuvek preparation.

Each carton contains one vial of suspension (1 mL extractable volume containing 5×10^9 PFU) and one vial of excipient gel (1.5 mL).

Concentration of the medicinal product is 2×10^9 PFU/mL after mixing.

Table 5. Preparation steps prior to administration

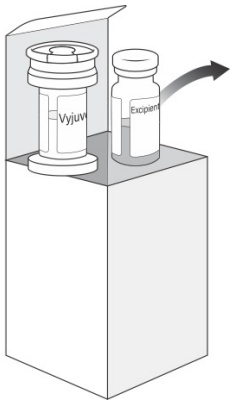
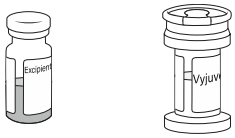
<table>
<tr><td rowspan="2">Before use, frozen vials must be removed from the carton and left at room temperature. (Step 1).

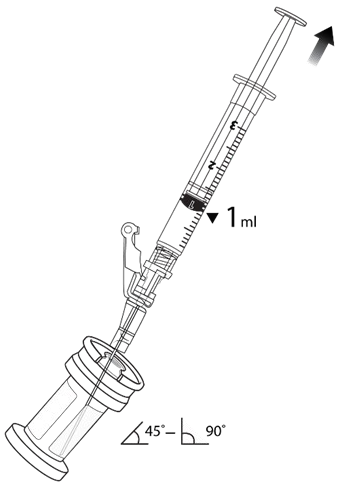
Once the vials are thawed (for approximately 30 minutes), they cannot be re-frozen. (Step 2)

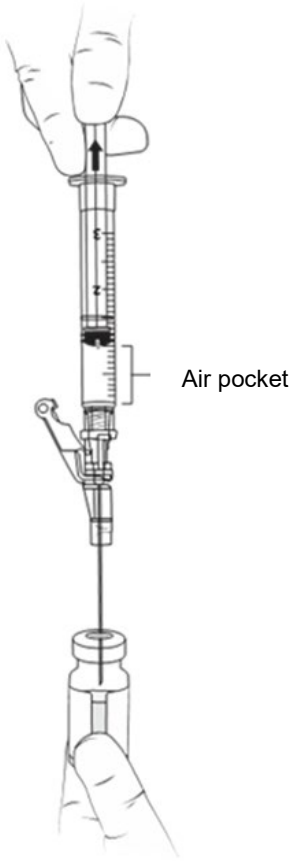
Visually inspect the suspension vial. The suspension may contain white to off-white particulates that are inherent to the product.
The suspension may vary in colour from opalescent yellow to colourless. Do not use this medication if you notice any discolouration.

Visually inspect the gel vial. The gel is a clear, colourless, viscous gel. Do not use the gel if you notice any particulates or discolouration.

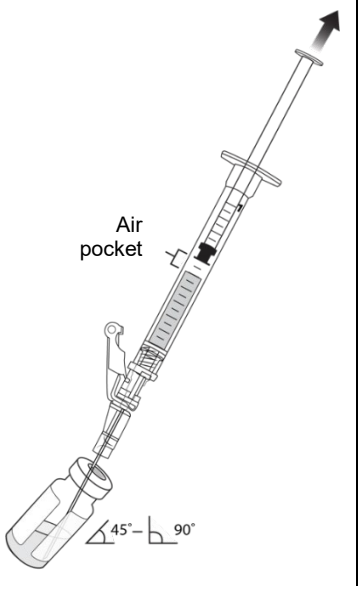
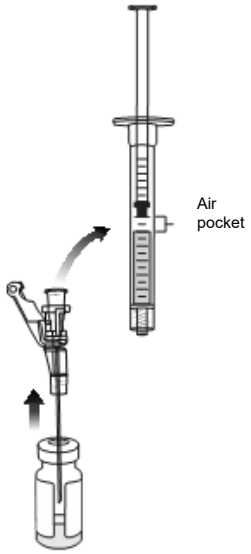
Gently invert the suspension vial 4-5 times to mix the contents.

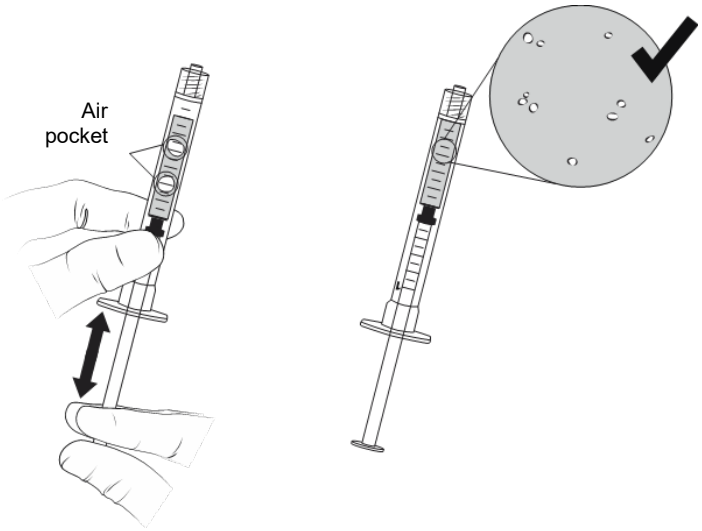
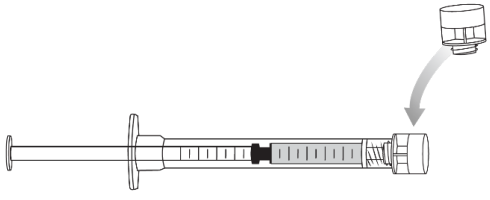
Remove the caps from the vials and clean each vial stopper with an alcohol pad. Allow them to dry.</td><td>Step 1</td><td>Step 2</td></tr>
<tr><td>  </td><td> 
Gel vial (left) Vyjuvek suspension vial (right)</td></tr>
<tr><td rowspan="2">Using an aseptic technique, withdraw 1 mL of thawed suspension (Step 1) using a 3 mL syringe and needle (e.g., 16G or 18G).

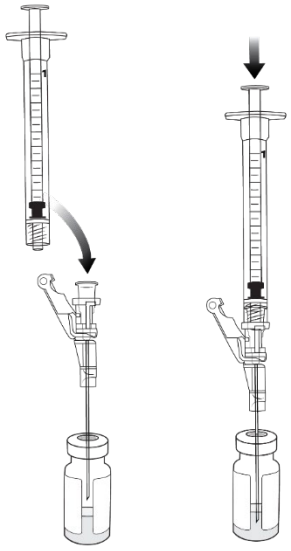
Transfer 1 mL of thawed suspension into the thawed gel vial.
(Step 2).</td><td>Step 1</td><td>Step 2</td></tr>
<tr><td> 
Vyjuvek suspension vial</td><td> 
Gel vial</td></tr>
</table>

Without removing the needle from the gel vial, pull the needle so it is above the liquid, remove 1 mL of air **(air pocket)** to vent the gel vial following the addition of the 1 mL of Vyjuvek suspension, and only then remove the syringe and needle and discard them. The vial with the combined suspension and gel will be referred to as the Vyjuvek vial for the remainder of these instructions.	 **Vyjuvek vial**

Place an alcohol pad on the gel vial stopper and shake the vial vigorously by hand for at least 10 seconds. The excipient gel should incorporate the suspension to form a homogeneous gel. Visually inspect the Vyjuvek vial. The gel containing the active substance may contain white to off-white particulates that are inherent to the product. The mixed product, like the suspension, may vary in colour from opalescent yellow to colourless. Do not use this medication if you notice any discolouration.	 **Vyjuvek vial**

Connect a new needle (e.g., 16G or 18G) to a 1 mL syringe and slowly withdraw 0.5 mL of Vyjuvek (**Step 1**). Do not invert the vial to withdraw the Vyjuvek syringe. Without removing the needle from the vial, lift the tip of the needle above the Vyjuvek and disconnect the syringe, leaving the needle within the vial stopper (**Step 2**). An **air pocket** may form, this is normal.	**Step 1**  	**Step 2** 
	Vyjuvek vial	

Gently manipulate the plunger up and down to remove the air pocket. DO NOT flick the syringe to remove the air pocket. Small bubbles may remain, this is normal.	
Cap the syringe and set aside.	

Obtain the next 1 mL syringe and connect it to the needle in the gel vial stopper and withdraw 0.5 mL of Vyjuvek, remove the air pocket and cap the syringe. Extractable volume is 2.0 mL (4×10^9 PFU). Repeat as applicable based on the recommended posology. Label the syringe with patient's ID, name of the product, lot number, EXP date, and storage conditions. Avoid covering the syringe marks needed for administration. Place the capped Vyjuvek syringes into a sealable plastic bag . Label the plastic bag with patient's ID, name of the product, lot number, EXP date, and storage conditions. No more than 2 mL (four 0.5 mL syringes) can be used in the same week as this is the maximum weekly dose.	

Place a sealable plastic bag with Vyjuvek syringes into an appropriate insulated tertiary container ("outer container") to maintain a transport temperature of 2°C to 8°C suitable for transport and in order to protect from light.

The outer container needs to be fully closed for transportation.

Open the outer container designed for transportation of prepared Vyjuvek syringes only at the site of administration.).

Reception and storage at administration site

After receipt of the outer container, store the outer container in a secure, room-temperature location that is clean, out of reach of children, and free from potential contamination.

Only the person responsible for the administration should open the outer container.

The person responsible for the administration should check that the outer container is intact and there are no signs of leakage before use (see section 4.2).

Measures to take in case of accidental exposure

In case of accidental exposure local guidance for pharmaceutical waste must be followed.

All surfaces that may have come in contact with beremagene geperpavec must be cleaned and all spills must be disinfected with a virucidal agent such as 70% isopropyl alcohol, 6% hydrogen peroxide or < 0.4% ammonium chloride.

In the event of an accidental exposure through a splash to the eyes or mucous membranes, flush with clean water for at least 5 minutes.

In the event of exposure to intact skin or needlestick injury, clean the affected area thoroughly with soap and water and/or a disinfectant.

Precautions to be taken for the disposal of the medicinal product

Any unused medicinal product or waste material (e.g., vial, syringe, needle, cleaning materials) that that may have come in contact with Vyjuvek should be disposed of in compliance with local guidance for pharmaceutical waste.

Disinfect dressings with a virucidal agent, such as 70% isopropyl alcohol, 6% hydrogen peroxide or < 0.4% ammonium chloride, and dispose of the disinfected dressings in a separate sealed plastic bag in household waste or according to local requirements.

7 MARKETING AUTHORISATION HOLDER

Krystal Biotech Netherlands, B.V.
Atrium Gebouw
Strawinskylaan 3051
Amsterdam 1077 ZX
Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1918/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Krystal Biotech, Inc.
2100 Wharton Street,
Suite 701
Pittsburgh, PA 15203 USA

Name and address of the manufacturer responsible for batch release

ProPharma Group The Netherlands B.V.
Schipholweg 73
2316 ZL Leiden
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Vyjuvek in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication

media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where Vyjuvek is marketed, all HCPs (pharmacists, prescribing physicians, and/or nurses) and patients/carers who are expected to prescribe, use, or oversee the administration of Vyjuvek have access to/are provided with the following educational packages aimed at highlighting the important potential risks of Vyjuvek. These packages will be translated into the local language to ensure understanding of proposed mitigation measures by all users.

HCP educational materials consist of

- Guide for HCPs
- Vyjuvek dose preparation video
- Vyjuvek administration video

Patient/Caregiver educational materials consist of

- Guide for patients and caregivers
- Vyjuvek administration video

Guide for HCP

The guide will explain the following

Preparation and administration

- Training on how to prepare and administer Vyjuvek, including a QR code with access to a preparation and administration video.
- Ability for the HCP to order a demonstration kit to facilitate the training of the HCP, patient, or caregiver.

Storage and Transport

- Appropriate storage conditions prior to and after mixing of Vyjuvek and handling of the drug
- Requirements for transport of prepared syringes to the setting of administration (including surveillance of temperature and timeline)

Administration objectives and patient/caregiver counselling

- The appropriate dosing and treatment plan
- Detailed information on treated wound dressing
- Steps to consider to prevent further accidental exposure
- Actions to take in the event of an accidental exposure and in case of emergency
- Appropriate biological waste management
- The HCP should provide and discuss the patient and caregiver guide with the patient/caregiver
- HCPs should encourage patients to participate in the long-term study PASS-01

Home setting

- Requirements for home administration, including availability and timely administration
- In case of in-home administration, the prescribing physician should establish a treatment plan, indicating the appropriate dose and prioritizing wounds to treat initially and sequential wounds to treat afterwards
- Suitability of the patient for home administration by HCP:
    - Training of HCP who will administer the product in home setting
    - Educating / counselling of patient and caregiver on home administration and discuss and provide the patient and caregiver guide
- Suitability of the patient for home administration by care giver or patient:

- Requirement for at least one application of Vyjuvek to be administered by patient/caregiver under the supervision of a HCP in a healthcare setting (or as many times as needed to be compliant with all steps)

Guide for patients and caregivers

The guide will explain the following

- Training administration video (QR code with access to administration video)
- How the administration of Vyjuvek is performed
- Steps to consider to prevent accidental exposure
- Actions to take in the event of an accidental exposure and in case of emergency
- Detailed information on treated wound dressing, including changing and disposing of wound dressings
- Appropriate biological waste management
- Encourage the patient to participate in the long-term study PASS-01

Home setting

- Requirements for home administration, including availability and timely administration
- Requirements for transport of prepared syringes to the setting of administration (including storage conditions and timeline)
- Appropriate storage conditions of Vyjuvek and handling of the drug
- In the case of home administration by a caregiver or patient, there will be a requirement for at least one application of Vyjuvek to be administered by patient/caregiver to take place under the supervision of a HCP in a healthcare setting(or as many times as needed to be compliant with all steps)
- The prescribing physician has established a treatment plan, indicating the appropriate dose and prioritizing wounds to treat initially and sequential wounds to treat afterwards

Vyjuvek dose preparation video

The video will explain: all steps necessary for mixing and preparing the Vyjuvek syringes for administration, including transport conditions of the prepared syringes to the setting for administration in accordance with the EU SmPC and package leaflet.

Vyjuvek administration video

The video will explain: all steps of administration including wound dressing and waste disposal in accordance with the EU SmPC and package leaflet and national guidelines on genetically modified and biological material.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): In order to further characterise the long-term safety of Vyjuvek in patients with dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene, including patients less than 6 months of age, the MAH should conduct and submit the results of a prospective, non-interventional, multi-country study in patients treated with Vyjuvek in a real-life clinical setting.	Final report: 31 December 2034

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Vyjuvek 5×10^9 plaque forming units/mL suspension and gel for gel
beremagene geperpavec

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 1 mL extractable volume of suspension containing 5×10^9 plaque forming units (PFU) of beremagene geperpavec.

3. LIST OF EXCIPIENTS

Excipients in suspension: E422, sodium chloride, E339, E508, E340.

Excipients in gel: E464, trometamol, sodium chloride, E339, and E340.

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Suspension and gel for gel

1 suspension vial, 1 mL
1 vial of 1.5 mL excipient gel

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Cutaneous use.
Thaw before use. Suspension must be mixed with gel before use.

QR code to be included
For more information scan QR code or visit: http://ema.krystallabel.com/

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store frozen at -15°C to -25°C.
Keep the vials in the outer carton prior to thawing in order to protect from light.
Shelf life after thawing: 1 month refrigerated (2°C to 8°C). Date of thawing __/__/__.
Once thawed, do not refreeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically modified organisms.
Dispose of in compliance with the local guidance for pharmaceutical waste.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Atrium Gebouw
Strawinskylaan 3051
Amsterdam 1077 ZX
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/25/1918/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL (SUSPENSION)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Vyjuvek 5×10^9 PFU/mL suspension for gel
beremagene geperpavec
Cutaneous use

2. METHOD OF ADMINISTRATION

Mix with gel before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mL

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL (GEL)

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Gel for Vyjuvek
Cutaneous use

2. METHOD OF ADMINISTRATION

Mix with suspension

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.5 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient, or carer

Vyjuvek 5×10^9 Plaque Forming Units/mL suspension and gel for gel
beremagene geperpavec

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

If you are the carer of a patient who will receive Vyjuvek, when "you" appears in this package leaflet, it refers to your charges except where it says otherwise.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1 What Vyjuvek is and what it is used for

Vyjuvek is a modified viral gene therapy. It contains the active substance beremagene geperpavec, a genetically modified virus encoding for the human protein COL7.

Vyjuvek is used to treat wounds in patients with a rare genetic disorder called dystrophic epidermolysis bullosa (DEB) with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene, which primarily affects the skin. It can be used from birth onward. DEB is caused by a faulty gene that affects the production of the COL7 protein, which glues the skin layers together. If this protein is missing or does not function appropriately, the layers of the skin will not join properly. This makes the skin very fragile and likely to blister.

Vyjuvek has been modified to make the virus contain working copies of the faulty gene found in patients with DEB. The medicine delivers these working copies of the gene into the cells of the wound to help the skin heal. The modified virus and genetic material in this medicine do not change your own DNA.

2 What you need to know before you are given Vyjuvek

You must not be given Vyjuvek:
- if you are allergic to beremagene geperpavec or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or nurse before you administer or you are administered Vyjuvek if you have a type of skin cancer called squamous cell carcinoma. Vyjuvek should not be applied to wounds with a

confirmed or suspected diagnosis of squamous cell carcinoma. In people who develop squamous cell carcinoma, Vyjuvek may still be applied to wounds on skin that has no confirmed or suspected squamous cell carcinoma.

Accidental contact with Vyjuvek

This medicine contains genetically modified organisms. Although it will not integrate with your own DNA, accidental exposure of area's other than wounded skin should be avoided.

You and/or your doctor or nurse should:

- Avoid direct contact with treated wounds (e.g., touching or scratching) and dressings of treated wounds for approximately 24 hours following treatment.
- Your doctor or nurse and your carer should wear personal protective equipment (e.g., gloves, mask, eye protection) when administering Vyjuvek and assisting with changing wound dressings and handling their disposal (e.g., gloves), see section 3 “How Vyjuvek is given”.

Long-term follow-up
Patients taking this medicine may take part in a study that looks at the long-term safety of this medicine. Talk to your doctor or nurse about this study and how you can participate.

Other medicines and Vyjuvek
Tell your doctor or nurse if you are taking, have recently taken, or might take any other medicines.

There is no information on how Vyjuvek could react with other medicines applied to your wounds. Do not apply other medicines to your wounds along with Vyjuvek. Once Vyjuvek has been cleaned from the wounds, routine care may resume.

If you have any further questions on the use of this medicine with other medicines, ask your doctor or nurse.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you might be pregnant, or are planning to have a baby, ask your doctor or nurse for advice before being treated with Vyjuvek or handling Vyjuvek.

The effects of this medicine on pregnancy and the unborn child are not known. The use of Vyjuvek is not recommended while you are pregnant.

Vyjuvek has not been studied in breast-feeding women. It is not known whether it passes into breast milk. It is important to tell your doctor or nurse if you are breastfeeding or plan to do so. They will then help you decide whether to stop breast-feeding, or whether to stop taking Vyjuvek, taking into account the benefit of breast-feeding to the baby and the benefit of Vyjuvek to you.

Driving and using machines
Vyjuvek is expected to have little to no effect on the ability to drive or use machines.

3 How Vyjuvek is given

Vyjuvek is for cutaneous use on wounds only. Vyjuvek is given once a week by a doctor or nurse either in a clinic or at home. If your doctor or nurse considers it appropriate, you or your carer may also apply the medicine after you/your carer have been properly trained.

Always use this medicine exactly as your doctor or nurse has told you. Check with your doctor or nurse if you are not sure.

The maximum recommended weekly dose of Vyjuvek for children less than 3 years is up to 1 mL (2×10^9 PFU).

The maximum recommended weekly dose of Vyjuvek for adults and children aged 3 years and above is up to 2 mL (4×10^9 PFU).

Wound area (cm^2)*	**Volume (mL)**
< 20	< 0.2
20 to < 40	0.2 to < 0.4
40 to 60	0.4 to < 0.6
60 to < 200	0.6 to < 2

PFU=plaque forming units

*Vyjuvek should be applied to the selected wound, in small droplets approximately 1-cm by 1-cm apart (width of a fingertip).

All wounds may not be possible to be treated at each treatment visit. Vyjuvek should be applied to wounds until they are closed before selecting new wound(s) to treat. Weekly treatment of previously treated wounds should be prioritised if they re-open. If no wounds are present, Vyjuvek should not be administered.

How to apply Vyjuvek

Your pharmacist will prepare Vyjuvek for you. Vyjuvek will be supplied to you in capped syringes. Make sure you have the correct number or syringes according to your recommended posology.

Wound preparation
The wounds should be gently cleaned before applying Vyjuvek.

- Gently remove any medicines and ointments at the wound area.
- Do not use products that may contain anti-viral agents. If you are unsure if something you use contains these agents, ask your doctor or nurse.

Syringe preparation
The Vyjuvek syringes will be dispensed from the pharmacy in a plastic bag within an appropriate insulated container for transport to the setting of administration (e.g., to the clinical setting or home setting) (see section 5 How Vyjuvek is stored).

After you receive the insulated container, you must store the container in a secure, room-temperature location that is clean and free from potential contamination.

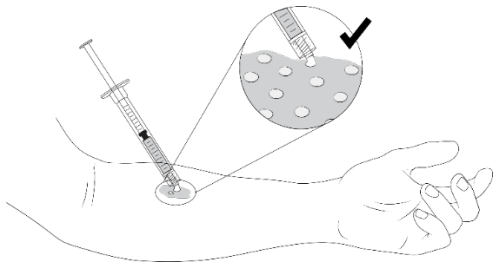
- Only the person responsible for the administration should open the container.
- The person responsible for the administration should check that the container is intact and there are no signs of leakage before use.

Pregnant women should not prepare or give Vyjuvek and should avoid direct contact with the skin where the medicine is applied or with dressings that have been in contact with the medicine.

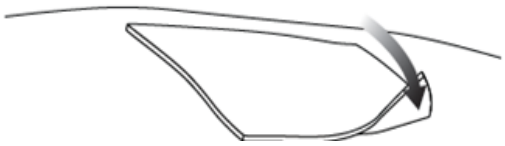
Personal protective equipment e.g., gloves, mask, and eye protection) should be worn when handling Vyjuvek.

Get the syringe ready.

- With each new syringe, before initial use, begin by pulling the plunger of the syringe down slightly, then gently pushing the plunger upwards toward the tip of the syringe.
- A small droplet of Vyjuvek should form at the tip of the syringe.

Apply Vyjuvek to the selected wound, in small droplets approximately 1-cm by 1-cm apart (width of a fingertip) with only the Vyjuvek droplet touching the wound. The tip of the syringe should not touch the skin to prevent the contamination of the gel in the syringe. The resulting droplet pattern should loosely resemble a grid. The amount of Vyjuvek applied may vary as the wound decreases or increases in size.	

Once Vyjuvek has been administered to the wound, cover the wound with a non-absorbent, water-repellent dressing (a dressing that will not absorb Vyjuvek). The dressing should be cut to a size slightly larger than the wound but may vary upon your preference. Once the Vyjuvek droplets are covered by the water-repellent dressing, a thin even layer of Vyjuvek will form within the wound.	

The standard wound care dressing should be cut to a size larger than the non-absorbent, water-repellent dressing. Cover the non-absorbent dressing with the standard dressing.	

Leave the dressing for approximately 24 hours after treatment.

Avoid touching or scratching treated wound areas or dressings.

Following the Vyjuvek dressing change, your routine care may resume.

Measures to take in case of accidental exposure
In the event of an accidental exposure (e.g., through a splash to the eyes or mucous membranes), flush with clean water for at least 5 minutes.

In the event of exposure to intact skin, clean the affected area thoroughly with soap and water and/or a disinfectant.

All working surfaces that may have come in contact with beremagene geperpavec must be cleaned and all spills must be disinfected with a virucidal agent such as bleach.

Syringe disposal

Any used or unused Vyjuvek syringe or material that that may have come in contact with Vyjuvek (e.g., gloves) should be disposed of in compliance with local guidance for pharmaceutical waste.

Changing and disposing of wound dressings

People changing (or assisting with changing) Vyjuvek wound dressings and handling their disposal should wear protective gloves.

All dressings that may have come into contact with Vyjuvek should be disinfected with an anti-viral agent, such as bleach. The disinfected bandages can be disposed in a separate sealed plastic bag in household waste or in accordance with local requirements.

Ask your doctor or nurse if you have questions after reading this package leaflet.

How long should you take Vyjuvek

You should continue using the medicine weekly until the wounds are closed. If previously treated wounds re-open, the medicine will be applied again. It may not be possible to apply Vyjuvek to all wounds at each treatment. If you do not have wounds, you should not receive treatment with Vyjuvek.

If you are given more Vyjuvek than you should have
There is limited clinical experience with overdose of Vyjuvek. In case of overdose, your doctor or nurse will treat the symptoms as necessary.

If you miss a dose of Vyjuvek
If a dose is missed, Vyjuvek should be administered as soon as possible, and weekly treatments will continue. It is not recommended to stop your treatment without first consulting your doctor or nurse.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most frequently occurring adverse reactions reported in the clinical study were:

Common (may affect up to 1 in 10 people)

- Itching of the skin
- Chills
- Reddening of the skin
- Rash of the skin
- Cough
- Runny nose

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5 How Vyjuvek is stored

You will receive the medicine in capped syringes within a sealable plastic bag, in an appropriate insulated container ("outer container") for transport. Store this medicine as recommended by your pharmacist.

Keep this medicine out of the sight and reach of children.

Your pharmacist is responsible for the adequate storage of the medicine. The following information is provided for your pharmacist.

Store frozen at -15°C to -25°C.
Keep the vials in the carton prior to thawing in order to protect from light.

After thawing the carton(s) may be stored in a refrigerator (2°C to 8°C) for up to 1 month.

After mixing chemical and physical in-use stability has been demonstrated for 168 hours (7 days) at 2 to 8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless mixing has taken place in controlled and validated aseptic conditions.

The syringes may be left at room temperature for up to 8 hours.

Do not use this medicine after the expiry date. The syringes may vary in colour from opalescent yellow to colourless. Do not use this medicine if you notice any discolouration.

Check with your doctor or nurse if you have any questions.

6 Contents of the pack and other information

What Vyjuvek contains

- The active substance is beremagene geperpavec. One vial contains 5×10^9 PFU of beremagene geperpavec suspension in 1 mL.
- The other ingredients are:
  - Suspension: glycerol (E422), sodium chloride, disodium phosphate (E339), potassium chloride (E508), dipotassium phosphate (E340).
  - Gel: hypromellose(E464), trometamol, sodium chloride, disodium phosphate (E339), dipotassium phosphate (E340).

What Vyjuvek looks like and contents of the pack

Vyjuvek 5×10^9 PFU/mL is a suspension and gel for gel.

<u>Suspension</u>

Opalescent yellow to colourless suspension following thaw from its frozen state. It is supplied in a cyclo-olefin copolymer vial with a thermoplastic elastomer closure and a green cap containing 1 mL of suspension.

<u>Gel</u>

Clear viscous gel, following thaw from its frozen state. It is supplied in a Type-1 glass vial with a bromobutyl elastomer stopper and a blue cap containing 1.5 mL of gel.

Each carton contains one vial of suspension and one vial of gel.

Marketing Authorisation Holder and Manufacturer

Krystal Biotech Netherlands, B.V.
Atrium Gebouw
Strawinskylaan 3051
Amsterdam 1077 ZX
Netherlands

Manufacturer
ProPharma Group The Netherlands B.V.
Schipholweg 73
2316 ZL Leiden
The Netherlands

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

Detailed information on administration of this product is also available by scanning the QR code included below or on the outer carton with a smart phone.
The same information is also available on the following URL: http://ema.krystallabel.com/
QR code to be included

The following information is intended for healthcare professionals (HCPs) only:

Refer to the Summary of Product Characteristics (SmPC) before using.

Preparation and administration of Vyjuvek

This medicine contains genetically modified organisms.

During preparation, administration, and disposal, appropriate precautions must be taken. Personal protective equipment (e.g., gloves, mask, and eye protection) should be worn when handling Vyjuvek.

HCPs or carers who are pregnant should not administer Vyjuvek and should not come into direct contact with treated wounds, or all material that has been in contact with treated wounds.

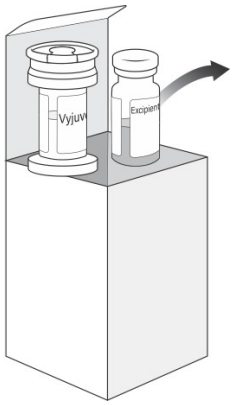
Preparation prior to administration

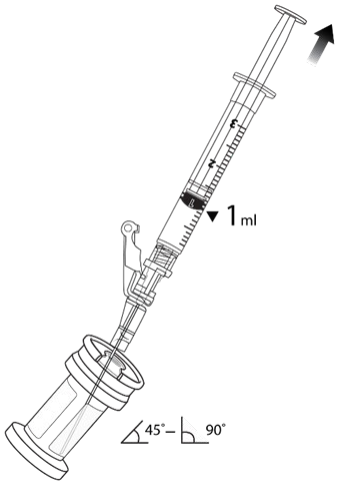
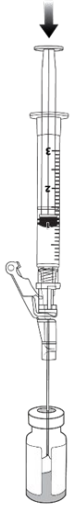
Follow the steps below for Vyjuvek preparation.

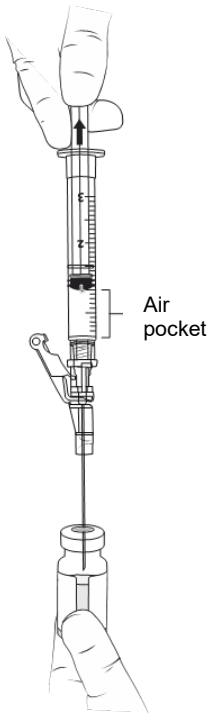
Each carton contains one vial of suspension (1 mL) and one vial of gel (1.5 mL)

Concentration of the medicinal product is 2×10^9 PFU/mL after mixing.

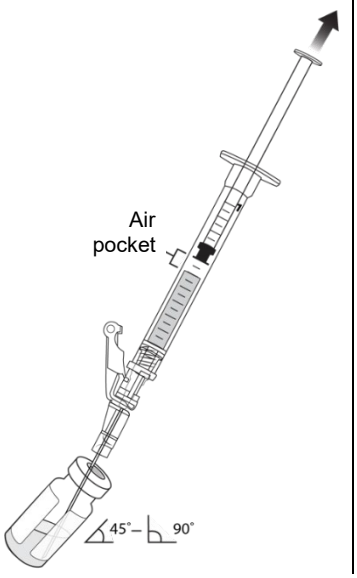
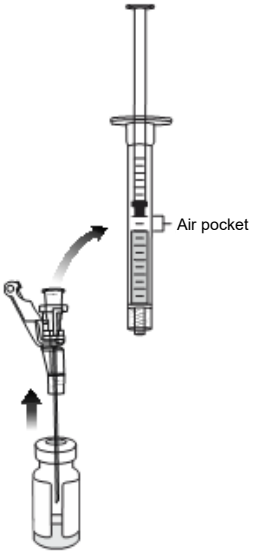
Table 1. Preparation prior to administration

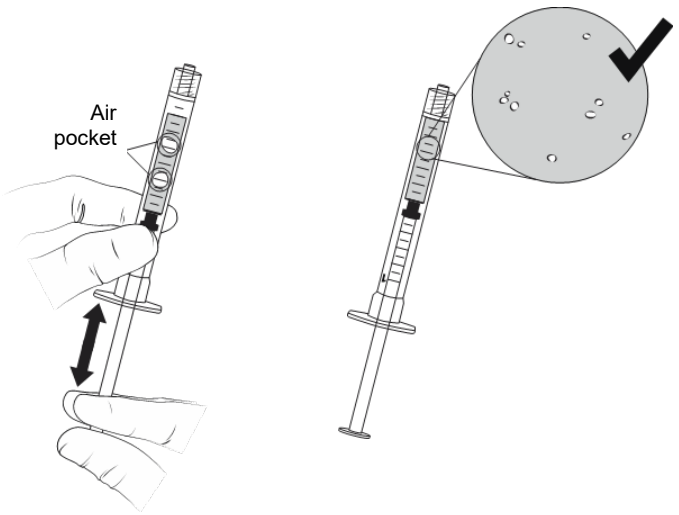
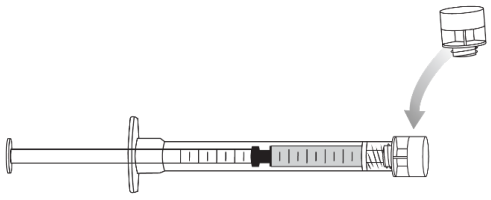
Before use, frozen vials must be removed from the carton and left at room temperature. (**Step 1**). Once the vials are thawed (for approximately 30 minutes), they cannot be re-frozen. (**Step 2**) Visually inspect the suspension vial. The suspension may contain white to off-white particulates that are inherent to the product. The suspension may vary in colour from opalescent yellow to colourless. Do not use this medication if you notice any particulates or discolouration. Visually inspect the gel vial. The gel is a clear, colourless, viscous gel. Do not use the gel if you notice any particulates or discolouration. Gently invert the suspension vial 4-5 times to mix the contents. Remove the caps from the vials and clean each vial stopper with an alcohol pad. Allow them to dry.	**Step 1**	**Step 2**
		  **Gel vial (left)** **Vyjuvek suspension vial (right)**

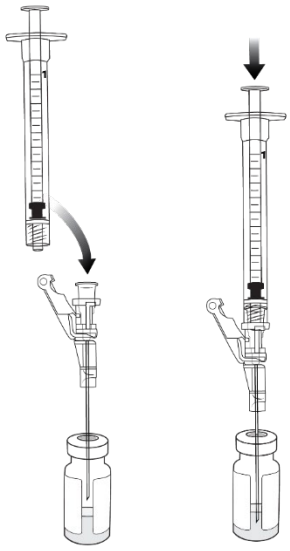
Using an aseptic technique, withdraw 1 mL of thawed suspension (**Step 1**) using a 3 mL syringe and needle (e.g., 16G or 18G). Transfer 1 mL of thawed suspension into the thawed gel vial (**Step 2**).	**Step 1**	**Step 2**
	 **Vyjuvek suspension vial**	 **Gel vial**

Without removing the needle from the gel vial, pull the needle so it is above the liquid, remove 1 mL of air **(air pocket)** to vent the gel vial following the addition of the 1 mL of Vyjuvek suspension, and only then remove the syringe and needle and discard them. The vial with the combined suspension and gel will be referred to as the Vyjuvek vial for the remainder of these instructions.	 **Vyjuvek vial**

Place an alcohol pad on the gel vial stopper and shake the vial vigorously by hand for at least 10 seconds. The excipient gel should incorporate the suspension to form a homogeneous gel. Visually inspect the Vyjuvek vial. The gel containing the active substance may contain white to off-white particulates that are inherent to the product. The mixed product, like the suspension, may vary in colour from opalescent yellow to colourless. Do not use this medicine if you notice any particulates or discolouration.	 **Vyjuvek vial**

Connect a new needle (e.g., 16G or 18G) to a 1 mL syringe and slowly withdraw 0.5 mL of Vyjuvek (**Step 1**). Do not invert the vial to withdraw the Vyjuvek syringe. Without removing the needle from the vial, lift the tip of the needle above the Vyjuvek and disconnect the syringe, leaving the needle within the vial stopper (**Step 2**). An **air pocket** may form, this is normal.	**Step 1**  	**Step 2**  **Vyjuvek vial**

Gently manipulate the plunger up and down to remove the air pocket. DO NOT flick the syringe to remove the air pocket. Small bubbles may remain, this is normal.	
Cap the syringe and set aside.	

Obtain the next 1 mL syringe and connect it to the needle in the gel vial stopper and withdraw 0.5 mL of Vyjuvek, remove the air pocket and cap the syringe. Extractable volume is 2.0 mL (4×10^9 PFU). Repeat as applicable based on the recommended posology. Label the syringe with patient's ID, name of the product, lot number, EXP date, and storage conditions. Avoid covering the syringe marks needed for administration. Place the capped Vyjuvek syringes into a sealable plastic bag . Label the plastic bag with patient's ID, name of the product, Lot number, EXP date, and storage conditions. No more than 2 mL (four 0.5 mL syringes) can be used in the same week as this is the maximum weekly dose.	

Place a sealable plastic bag with Vyjuvek syringes into an appropriate insulated tertiary container ("outer container") to maintain a transport temperature of 2°C to 8°C suitable for transport and in order to protect from light.

The outer container needs to be fully closed for transportation.

Open the outer container designed for transportation of prepared Vyjuvek syringes only at the site of administration.

Measures to take in case of accidental exposure

All surfaces that may have come in contact with beremagene geperpavec must be cleaned and all spills must be disinfected with a virucidal agent such as 70% isopropyl alcohol, 6% hydrogen peroxide or <0.4% ammonium chloride.

In the event of an accidental exposure (e.g., through the splash to the eyes or mucous membranes), flush with clean water for at least 5 minutes.

In the event of exposure to intact skin or needlestick injury, clean the affected area thoroughly with soap and water and/or a disinfectant.

Precautions to be taken for the disposal of the medicinal product

Disinfect bandages from the first dressing change with a virucidal agent, such as 70% isopropyl alcohol, 6% hydrogen peroxide or <0.4% ammonium chloride, and dispose of the disinfected bandages in a separate sealed plastic bag in household waste or according to local requirements.

Any used or unused Vyjuvek syringe or material that that may have come in contact with Vyjuvek (e.g., needles, syringes, gloves, etc.) should be disposed of in compliance with local guidance for pharmaceutical waste.