Pharmacy Manual for

the Dose Preparation of LUXTURNA®▼ (voretigene neparvovec)

IMPORTANT

This medicine contains a genetically modified organism.

Voretigene neparvovec should be prepared by pharmacists who have received training on the preparation of this gene therapy product.

The information in this manual is correct as of November 2020. If you have questions about the preparation of voretigene neparvovec, please contact your Novartis representative.

▼This medicinal product is subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk profile of the medicinal product. All suspected adverse reactions should be reported to HPRA Pharmacovigilance at www.hpra.ie. Adverse events can also be reported to Novartis preferably at www.novartis.com/report, by emailing drugsafety.dublin@novartis.com or by calling (01) 2080 612.

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Contents

Purpose of the Pharmacy Manual

Voretigene neparvovec is indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.

This Pharmacy Manual provides information to pharmacy personnel on the preparation of voretigene neparvovec in accordance with the Summary of Product Characteristics or product information approved in your country. The purpose of this educational programme is to ensure the correct use of voretigene neparvovec in order to minimise the risks associated with its administration and/or the administration procedure.

These risks include:

- increased intraocular pressure
- retinal tear
- retinal detachment
- macular disorders
- cataracts
- intraocular inflammation and/or infection related to the procedure
- accidental exposure to genetically modified organisms
- vitreous opacities

Special precautions for disposal and other handling

Avoid accidental exposure and follow universal biohazard precautions for preparation, administration and handling of voretigene neparvovec.

- Wear personal protective equipment (e.g. laboratory coat, safety glasses, and gloves) while preparing or administering voretigene neparvovec.
- Avoid accidental exposure to voretigene neparvovec, including contact with skin, eyes, and mucous membranes. Cover any exposed wounds before handling.
- Treat all voretigene neparvovec spills with a virucidal agent such as 1% sodium hypochlorite and blot using absorbent materials.
- Dispose of all materials that may have come in contact with voretigene neparvovec (e.g. vial, syringe, needle, cotton gauze, gloves, masks, or dressings) in accordance with universal biohazard precautions.

Accidental exposure

- **In the event of an accidental occupational 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 broken skin or needle stick injury, clean the affected area thoroughly with soap and water and/or a disinfectant.**

This medicine contains genetically modified organisms. Unused medicine must be disposed of in compliance with the institutional guidelines for genetically modified organisms or biohazardous waste, as appropriate.

Dose Preparation

Dosage forms and strengths

Each mL of concentrate contains 5 x 10^{12} vector genomes (vg). Each single-dose 2 mL vial of voretigene neparvovec contains 0.5 extractable mL of concentrate solution for subretinal injection, which requires a 1:10 dilution prior to administration. Each dose of voretigene neparvovec contains 1.5 x 10^{11} vg in a deliverable volume of 0.3 mL.

Required materials

The following materials are required for dilution and administration syringe preparation:

- One single-use vial of voretigene neparvovec
- Two 2-mL vials of solvent
- One 3-mL sterile syringe
- One 20G, 1-in sterile needle
- Three 1-mL sterile syringes
- Three 27G ½-in sterile needles
- Two sterile syringe caps
- One 10-mL sterile empty glass vial
- One sterile utility drape
- One sterile plastic bag
- Two sterile labels for administration syringes
- One sterile plain label
- Two sterile skin markers

The storage temperature of the concentrate and solvent is ≤-65°C. Following thawing of the vials, leave at room temperature.

Table 1 lists a commercially available syringe that has been tested in biocompatibility experiments for use with voretigene neparvovec. Figure 1 shows this syringe.

Table 1. Sterile biocompatible syringe

Product description	Manufacturer	Reference number
BD Luer-Lok™ 1-mL disposable syringe Has 1/100 mL graduations	Becton, Dickinson & Company Franklin Lakes, NJ	309628

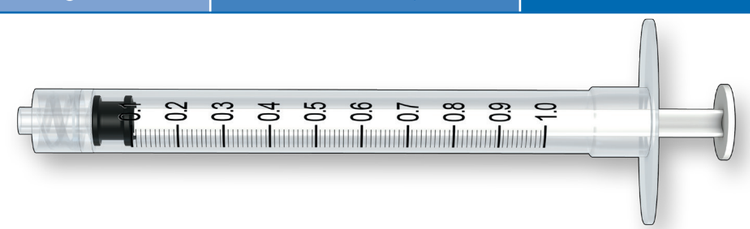

Figure 1. Representative syringe (model shown: BD Luer-Lok™ 1-mL disposable syringe, Franklin Lakes, NJ; reference number 309628)
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Dilution

IMPORTANT

Always use sterile technique under aseptic conditions in a Class II vertical laminar flow BSC to prepare voretigene neparvovec for administration.

1 Thaw the contents of the carton, 1 single-dose vial of voretigene neparvovec and 2 vials of solvent, at room temperature. Inspect the vials for damage. Ensure the voretigene neparvovec and solvent vials are within expiry. Mix the contents of the thawed solvent vials by gently inverting them approximately 5 times and inspect the solvent vials for particulates, cloudiness, or discoloration. Any anomalies or appearance of visual particulates should be reported to the Marketing Authorisation Holder and product should not be used.

IMPORTANT

Inspect the vials for any particulates, cloudiness, or discoloration after thawing. If particulates, cloudiness, or discoloration are visible, do not use the vial or vials.

2 Obtain a 3-mL sterile syringe, a 20G 1-in sterile needle, and a 10-mL sterile empty glass vial.

3 Transfer 2.7 mL of the solvent to the 10-mL glass vial using the 3-mL sterile syringe with the 20G 1-in sterile needle by sequential transfer of 1.4 mL and 1.3 mL volumes from the two vials of solvent, respectively. Dispose of the needle and syringe in an appropriate sharps container.

4 Mix the contents of the thawed voretigene neparvovec single-dose vial by inverting gently approximately 5 times.

5 Inspect the voretigene neparvovec single-dose vial for particulates, cloudiness, or discoloration. The solution should be clear to slightly opalescent.

IMPORTANT

If particulates, cloudiness, or discoloration are visible, do not use the vial; a new single-dose vial of voretigene neparvovec should be used. Any anomalies or appearance of visual particulates should be reported to the Marketing Authorisation Holder.

6 Draw 0.3 mL of voretigene neparvovec into a 1-mL sterile syringe with a 27G ½-inch sterile needle.

7 Transfer 0.3 mL of voretigene neparvovec to the 10-mL sterile glass vial containing 2.7 mL of diluent from Step 3. Dispose of the needle and syringe in an appropriate sharps container. Gently invert the 10-mL glass vial approximately 5 times to mix the contents. Inspect for any visual particulates. The diluted solution should be clear to slightly opalescent.

IMPORTANT

Mix the contents of the vial containing voretigene neparvovec and solvent by gently inverting the vial approximately 5 times.

8 Using the sterile plain label and sterile skin marker, label the 10-mL glass vial containing the diluted voretigene neparvovec as follows: “diluted voretigene neparvovec”.

9 Remove all items from the BSC except the glass vial labelled “diluted voretigene neparvovec”. Resanitize the BSC prior to the next steps and place the glass vial to the left side in the BSC.

Preparation of voretigene neparvovec
for subretinal injection

Dose preparation of voretigene neparvovec should be performed within 4 hours of beginning the administration procedure in accordance with the following recommended procedures, performed under aseptic conditions in a Class II vertical laminar flow biological safety cabinet (BSC).

Two operators are required for transfer of 0.8 mL of voretigene neparvovec from the 10-mL glass vial labelled “diluted voretigene neparvovec” into each of the two 1-mL sterile syringes. The objective is to ensure that the syringes remain sterile, including the external surfaces of the syringes that will be handled by the surgeon.

The Primary Operator will withdraw 0.8 mL of diluted voretigene neparvovec into each of two sterile 1-mL syringes and then place both syringes in a sterile plastic bag. The Primary Operator will touch only sterile surfaces, and his or her hands will stay within the BSC throughout the preparation and packaging of the two 1-mL sterile syringes containing voretigene neparvovec. The Secondary Operator will unwrap the required materials in a manner that prevents a breach of the sterility of the packaged contents.

IMPORTANT

Maintain sterility at all times and follow aseptic techniques.

1 Place a sterile utility drape, a sterile plastic bag, a sterile skin marker, and 2 sterile labels into the BSC. The Primary Operator changes to a new pair of sterile gloves. Place the sterile utility drape near the Primary Operator on the right side of the sanitized BSC surface, away from the diluted voretigene neparvovec. The Secondary Operator unwraps the items in the BSC, including the two 1-mL sterile syringes, two 27G ½-in sterile needles, and 2 sterile syringe caps, ensuring that the Primary Operator touches only sterile surfaces while transferring the items onto the sterile utility drape.

2 Prior to the next step, the Secondary Operator changes to a new pair of sterile gloves and positions himself or herself to the left of the Primary Operator. The Secondary Operator holds the 10-mL glass vial labelled “diluted voretigene neparvovec” during step 3 as shown below (Figure 2a.).

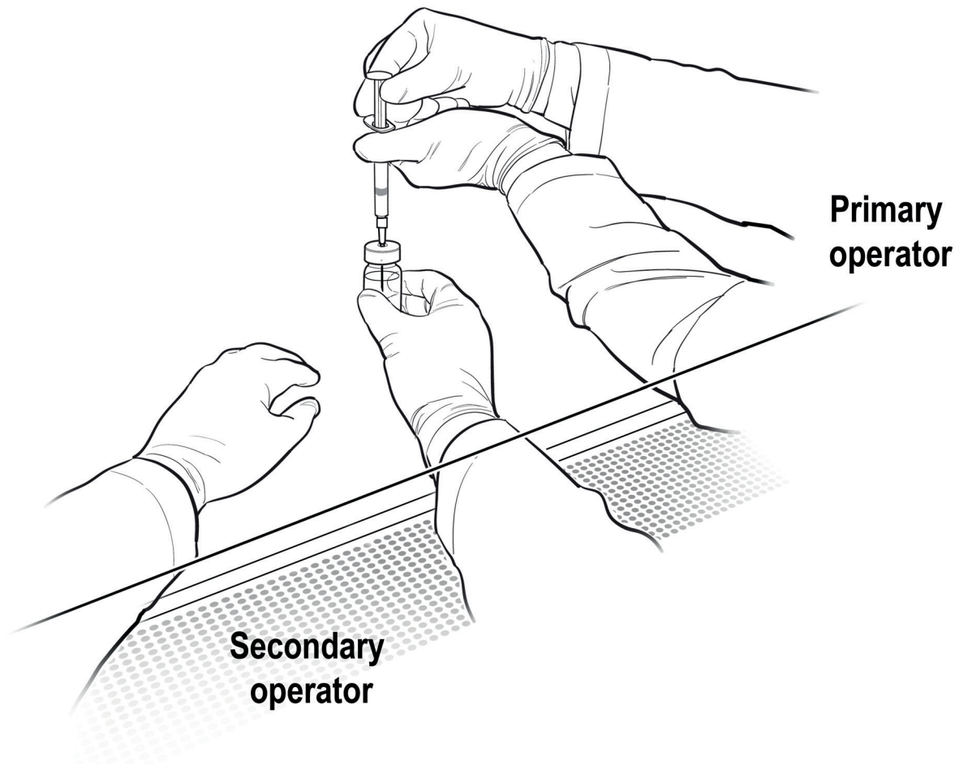

Figure 2a. First position of the operators during preparation of voretigene neparvovec administration syringes.

3 The Primary Operator withdraws 0.8 mL of the diluted voretigene neparvovec into a 1-mL sterile syringe using a 27G ½-in sterile needle while the Secondary Operator holds the 10-mL glass vial. After insertion of the needle (Figure 2a), the Secondary Operator inverts the 10-mL glass vial enabling the Primary Operator to withdraw 0.8 mL without touching the surfaces of 10-mL glass vial (Figure 2b).

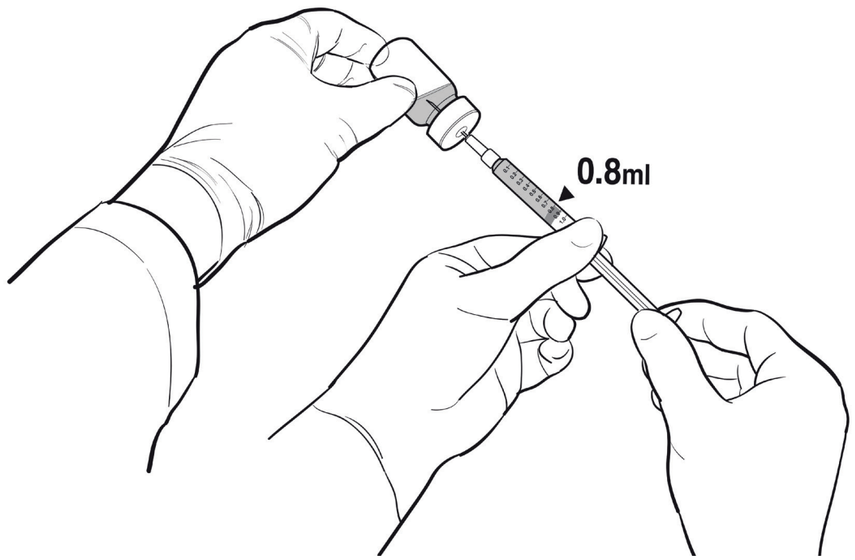

Figure 2b. Second position of the operators during preparation of voretigene neparvovec administration syringes.

4 The Primary Operator removes the needle and affixes a sterile syringe cap to the sterile syringe, disposes of the needle in an appropriate container, and attaches a sterile label to the administration syringe. Affix the label in a manner that the graduations on the syringe are not obscured and are clearly visible.

5 The Primary Operator repeats the previous 2 steps to prepare a total of 2 administration syringes. Label the first syringe "diluted voretigene neparvovec" and label the second syringe "Back-up diluted voretigene neparvovec" using the sterile skin marker. The second syringe will serve as a back-up for the surgeon performing the subretinal administration procedure. Discard the back-up syringe after surgery if not used.

6 Inspect both syringes.

IMPORTANT

Prepare a total of 2 syringes, with one serving as a back-up for the surgeon. Discard the back-up syringe after surgery if not used. The first syringe and second back-up syringe must be available for the surgeon performing the subretinal administration.

7 The Primary Operator places the two 1-mL sterile syringes each containing 0.8 mL of the diluted voretigene neparvovec into a sterile plastic bag in an aseptic manner and seals the bag.

IMPORTANT

If particulates, cloudiness, or discoloration are visible, do not use the syringe. Do not proceed if a back-up syringe is not available for the surgeon performing the subretinal administration.

8 Place the sterile plastic bag with syringes each containing diluted voretigene neparvovec into an appropriate secondary container (e.g. hard plastic cooler) for delivery to the surgical suite at room temperature.

IMPORTANT

Dispose of all materials that may have come in contact with voretigene neparvovec in accordance with local biohazard waste disposal guidelines.

References

1. Novartis Europharm Limited (2019) LUXTURNA® Summary of Product Characteristics.
2. Data on File_1. 2019. Study report of a biocompatibility assessment for the 1mL syringe and glass vial used during voretigene neparvovec preparation and dilution.
3. Data on File_2. 2019. Study report of a biocompatibility assessment for the 1mL syringe and glass vial used during voretigene neparvovec preparation and dilution.
4. Data on File_3. 2019. Clinical protocol of a drug administration and dosing study, including naming the reference number for the 1mL syringe to be used and specifying handling procedure of voretigene neparvovec.

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LUXTURNA®
voretigene neparvovec
for subretinal injection

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