Important Safety Information for Healthcare Professionals
About CASGEVY® ▼ (exagamglogene autotemcel)

Handling and Administration Guide

This guide is part of the marketing authorisation and provides important information on the handling and administration of CASGEVY to ensure its safe and effective use.

It does not contain all the information about this product. Please always consult the Summary of Product Characteristics for full prescribing information.

CASGEVY (exagamglogene autotemcel) is a genetically modified autologous CD34+ cell enriched population that contains human haematopoietic stem and progenitor cells (HSPCs) edited *ex vivo* by CRISPR/Cas9 at the erythroid-specific enhancer region of the *BCL11A* gene.

CASGEVY is approved for the following indications:

- **Treatment of transfusion dependent β-thalassemia (TDT) in patients 12 years of age and older.**
- **Treatment of sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs).**

Version 1.0
Date of Preparation: May 2024

casgevy® ▼
(exagamglogene autotemcel)

Approved by the Saudi Food and Drug Authority May 2024

1. Precautions to take before handling and administering CASGEVY

- This medicinal product contains human blood cells. Healthcare professionals handling CASGEVY should take appropriate precautions (wearing gloves, protective clothing and eye protection) to avoid potential transmission of infectious diseases.

2. Receipt and storage of CASGEVY

- CASGEVY is shipped to the treatment centre frozen in the vapour phase of liquid nitrogen.
- Confirm patient identifiers on the product label(s) and lot information sheet.
- If there are any concerns about the product or packaging upon receipt, contact Vertex Pharmaceuticals at 800-844-3907.
- Store in the vapour phase of liquid nitrogen at ≤ –135 °C until ready for thaw and administration.

3. How to prepare for CASGEVY infusion

- Coordinate the timing of CASGEVY thaw and infusion. Confirm the infusion time in advance and adjust the start time for thaw so that CASGEVY is available for infusion when the patient is ready, as CASGEVY must be administered within 20 minutes of thawing the vial. Thaw and infuse one vial at a time.
- Assemble supplies needed to thaw and withdraw the product from the vial(s). With the exception of the water bath, these supplies are single use. Assemble sufficient supplies for each vial to be administered:
  - Water bath
  - Alcohol swabs
  - Vial adapter (to allow for needle-less extraction)
  - 18 micron stainless steel filter
  - 30 mL luer-lock syringe
  - 0.9% sodium chloride (saline, 5 to 10 mL needed for each vial)
  - 10 mL luer-lock syringe for saline rinse

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4. How to check CASGEVY vials prior to thawing

- Before thaw, **confirm the patient's identity matches the patient information on the CASGEVY vial(s).**
- Do not remove the CASGEVY vials from cryo-storage if the information on the patient-specific label does not match the intended patient.
- A dose of CASGEVY may be contained in one or more cryopreserved patient-specific vial(s). **Account for all vials and confirm each vial is within the expiry date using the accompanying lot information sheet.**
- Inspect the vial(s) for any breaks or cracks prior to thawing. If a vial is compromised, do not infuse the contents. Call Vertex Pharmaceuticals at 800-844-3907.

5. How to thaw CASGEVY

- When the dose consists of multiple vials, thaw and administer one vial at a time. Whilst thawing a vial, remaining vials must remain in cryo-storage at ≤ -135 °C.
- Thaw each vial at 37 °C using a water bath. Ensure water bath temperature does not exceed 40 °C.
- Thaw each vial holding the vial neck, gently agitating clockwise and counterclockwise. This can take between 10 to 15 minutes.
- Do not leave vial unattended during thaw.
- Thawing is complete when ice crystals are no longer visible in the vial.
- Remove vial from water bath immediately once thawed.
- The thawed product should appear as a translucent cell dispersion, which may contain visible particles.
- Infuse within 20 minutes of thaw.

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6. How to administer CASGEVY

CASGEVY is for autologous use only. The patient's identity must match the patient identifiers on the CASGEVY vial(s). Do not infuse CASGEVY if the information on the patient-specific label does not match the intended patient.

A patient's dose may consist of multiple vials. All vials must be administered. The entire volume of each vial provided should be infused. If more than one vial is provided, administer each vial completely before proceeding to thaw and infuse the next vial.

- CASGEVY must be administered between 48 hours and 7 days after the last dose of myeloablative conditioning.
- It is recommended that pre-medication with paracetamol (antipyretics) and an antihistamine (e.g., diphenhydramine hydrochloride) be administered per institutional guidelines, before the infusion of CASGEVY, to reduce the possibility of a hypersensitivity reaction. CASGEVY is administered as an intravenous bolus (IV push) through a central venous catheter. The total volume of CASGEVY administered within one hour must not exceed 2.6 mL/kg.
- Please consult the Summary of Product Characteristics Section (SPC) 6.6 for information on attaching the vial adapter and filter as well as withdrawal of CASGEVY from the vial. The optional product/patient identifier label can be peeled from the lot information sheet and affixed to the syringe.
- CASGEVY must be administered within 20 minutes of product thaw.
- Perform a **two-person confirmation and verification of patient's identification at the bedside prior to the infusion of each vial(s).**
- Do not use an inline filter when infusing CASGEVY.
- After administration of each vial of CASGEVY, flush the primary line with 0.9% sodium chloride solution.

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7. Additional information regarding mobilisation, apheresis, and pre-treatment conditioning

Mobilisation and apheresis

- Patients are required to undergo CD34+ HSPC mobilisation followed by apheresis to isolate the CD34+ cells for medicinal product manufacturing.

- Each mobilisation and apheresis cycle must be separated by a minimum of 14 days.

- In patients with TDT:
  - Prior to apheresis procedure, it is recommended that patients receive red blood cell (RBC) transfusion(s) with a goal to maintain total haemoglobin (Hb) concentration ≥ 11 g/dL.
  - Granulocyte colony-stimulating factor (G-CSF) dosage should be reduced for splenectomised patients per local/institutional guidelines.

- In patients with SCD:
  - Prior to apheresis it is recommended that patients receive RBC exchange or simple transfusions to achieve target HbS levels < 30% of total Hb while keeping total Hb concentration ≤ 11 g/dL, for a minimum of 8 weeks before the planned start of mobilisation.
  - At initiation of RBC exchange or simple transfusions, discontinue disease modifying therapies (e.g., hydroxyurea/hydroxycarbamide, crizanlizumab, voxelotor).
  - G-CSF should NOT be administered for mobilisation in patients with SCD.

Pretreatment conditioning

- Full myeloablative conditioning must be administered before infusion of CASGEVY. Consult prescribing information for the myeloablative conditioning agent(s) prior to treatment.

- If busulfan is used as a single agent for myeloablation, there are important considerations regarding administration. Key points are outlined below.
  - Busulfan should be administered for 4 consecutive days intravenously via a central venous catheter at a starting dose of 3.2 mg/kg/day once daily or 0.8 mg/kg every 6 hours. Busulfan plasma levels should be measured by serial blood sampling and the dose adjusted to maintain exposure in the target range:
    - For once daily dosing, the four-day target cumulative busulfan exposure of 82 mg*h/L (range 74 to 90 mg*h/L), corresponding to $AUC_{0\text{-}24h}$ of 5000 µM*min (range: 4500 to 5500 µM*min).
    - For dosing every 6 hours, the four-day target cumulative busulfan exposure of 74 mg*h/L (range 59 to 89 mg*h/L), corresponding to $AUC_{0\text{-}6h}$ of 1125 µM*min (range 900 to 1350 µM*min).

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- In patients with TDT, if transfusions were not continued to maintain Hb at ≥ 11 g/dL after apheresis, reinitiate at least 60 days prior to myeloablative conditioning to achieve the same target total Hb levels.

- In patients with SCD:
  - If exchange or simple transfusions were paused after apheresis, reinstate for at least the 8 weeks prior to the start of myeloablative conditioning, to achieve the same target total Hb and HbS (%) levels.
  - At initiation of RBC exchanges or simple transfusions, discontinue disease modifying therapies (e.g., hydroxyurea/hydroxycarbamide, crizanlizumab, voxelotor).

- Iron chelation therapy should be stopped at least 7 days prior to myeloablative conditioning.

- Prophylaxis for seizures should also be considered. Refer to the prescribing information of the conditioning agent used for information on drug interactions.

- Prophylaxis for hepatic venoocclusive disease (VOD)/hepatic sinusoidal obstruction syndrome should be considered, per institutional guidelines.

8. Reporting of adverse drug reactions (ADRs)

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 drug reactions to the National Pharmacovigilance Centre (NPC):

- Saudi Food and Drug Authority Call Center: 19999

- E-mail: npc.drug@sfda.gov.sa

- Website: https://ade.sfda.gov.sa/

Any suspected adverse reactions to CASGEVY should also be reported to Vertex Pharmaceuticals on 800-844-3907 or at reportAE@vrtx.com.

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Additional copies of this guide will be available upon request.