Package leaflet: Information for the patient or carer

Casgevy 4-13 × 10^6 cells/mL dispersion for infusion
exagamglogene autotemcel ($CD34^+$ cells)

▼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.

Read all of this leaflet carefully before you are given 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 Casgevy is and what it is used for

What Casgevy is

Casgevy is a cell therapy, which is given to you once only as a blood stem cell transplant. It is made from your own blood stem cells and is made specifically for you. Blood stem cells can turn into other blood cells including red cells, white cells and platelets. Cells are taken from you, then are modified and given back to you as a transplant in a hospital.

What Casgevy is used for

Casgevy is used to treat:
- **People over 12 years of age with beta-thalassemia** who need regular blood transfusions. People with beta-thalassemia do not have enough haemoglobin, a protein in the blood that carries oxygen throughout the body. This causes anaemia, and they need regular blood transfusions.
- **People over 12 years of age with sickle cell disease** who have frequent painful crises (called vaso-occlusive crises). Patients with sickle cell disease have a different form of haemoglobin from other people (sickle cell haemoglobin). It produces abnormal sickle-shaped red blood cells, and these can lead to the blockage of blood vessels, causing vaso-occlusive crises.

How Casgevy works

Casgevy works by increasing the production of a special type of haemoglobin called Haemoglobin F (*foetal haemoglobin*). Having more Haemoglobin F increases haemoglobin levels in the body and improves the production and function of red blood cells. This can mean that people with beta-thalassemia may not need blood transfusions. For people with sickle cell disease, it can also reduce or even stop their vaso-occlusive crises.

2. What you need to know before you are given Casgevy

You must not be given Casgevy:

- **if you are allergic to exagamglogene autotemcel** or any of the other ingredients in this medicine (listed in section 6).
- **If you are allergic to any of the ingredients** in the mobilisation or conditioning medicines you will be given before treatment with Casgevy (see section 3)

Tell your doctor straight away if either of these applies to you. The treatment will not be given to you.

Warnings and precautions

Talk to your doctor or nurse before you are given Casgevy.

Before treatment with Casgevy:

- You will have **two other types of medicine** before you are given Casgevy. For more information on these medicines, see section 3.
    - **Mobilisation medicine** that moves the blood stem cells into the blood stream, allowing them to be collected to make Casgevy. This will take 2-6 days.
    - **Conditioning medicine** to clear cells from the bone marrow, shortly before you are given Casgevy.
- The doctor will discuss the **possible impact of the conditioning medicine on fertility**. See below under "*Fertility in men and women*".

After treatment with Casgevy:

- You will have fewer blood cells for a while, until Casgevy takes hold in your bone marrow. This includes:
    - Low levels of platelets, cells that usually help the blood to clot. Low levels may cause bleeding.
      Tell your doctor right away if you have any of these signs of low platelet cell levels: severe headache, abnormal bruising, prolonged bleeding, or bleeding without injury such as nosebleeds, bleeding from gums, blood in your urine, stool, or vomit, or coughing up blood.
    - Low levels of white blood cells that usually prevent infections. Low levels may make infections more likely.
      Tell your doctor right away if you have any of these signs of low white blood cell levels: fever, chills, or infections.
- Your doctor will monitor blood cell levels and give you treatment as required. The doctor will tell you when they return to safe levels.

- **You must not donate** blood, organs, tissues or cells.

- The doctor will monitor your blood cell levels and overall health to help understand the long-term effects of Casgevy.

Casgevy is made from your own cells and is only given to you. Information about cell-based medicinal products must be kept for 30 years at the hospital where you receive the treatment. The information they keep will include your name, name of the product and the batch number(s) of Casgevy you received.

If Casgevy treatment cannot be completed or fails

If Casgevy cannot be given after the conditioning medicine, or if the modified blood stem cells do not take hold in the body, the doctor may decide to return your own original blood stem cells (rescue cells) that are collected and stored before treatment starts (see section 3). If you are given rescue cells, you will not have any treatment benefit and will still need treatment for either beta-thalassemia or sickle cell disease.

Children under 12 years of age

Casgevy is not to be given to children under 12. It is not yet known if Casgevy is safe and effective in these children.

Other medicines and Casgevy

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

Do not take medicines that remove iron from your body (chelating agents) for at least 7 days before you are given the conditioning medicine. Your doctor will advise you if and when you can start taking these medicines after Casgevy treatment.

Do not take other medicines for sickle cell disease (such as hydroxyurea/hydroxycarbamide, crizanlizumab or voxelotor) for at least 8 weeks before you are given the mobilisation and conditioning medicines. Your doctor will advise if and when you should start taking these medicines after Casgevy treatment.

Talk to your doctor if you need to have any **vaccinations**.

Pregnancy, breast-feeding and fertility

- **Pregnancy**
  This treatment is not to be given during pregnancy because of the possible effects of the conditioning medicine. The effects of Casgevy in pregnant women are not known. Talk to your doctor about pregnancy after receiving Casgevy.

  If you are pregnant or think you may be pregnant after treatment with Casgevy, **talk to your doctor immediately.**

  If you are a woman who can get pregnant, **you will be given a pregnancy test** before starting mobilisation and conditioning medicines to make sure you are not pregnant.

- **Contraception in men and women**
  If you are a woman who can get pregnant, or a man capable of fathering a child, **you must use an effective method of contraception** from the start of mobilisation and **for at least 6 months** after receiving Casgevy. Talk to your doctor about which methods of contraception are appropriate.

- **Breast-feeding**
  Breast-feeding must be stopped during conditioning because of the possible effects of the conditioning medicine. It is not known whether the ingredients of Casgevy can pass into breast milk. Your doctor will consider the benefit of breast-feeding for your baby and the benefit of treatment for you to help you decide whether you can breast-feed after Casgevy treatment.

- **Fertility in men and women**
  It may not be possible for you to become pregnant or father a child after you have had the conditioning medicine. **You should discuss your options with your doctor before treatment.** These may include storing reproductive material (for instance, eggs, sperm) to use at a later time.

Driving and using machines

The mobilisation medicine and conditioning medicines used before Casgevy treatment may cause dizziness and fatigue. If you feel dizzy, tired, or unwell, do not drive, use machines or take part in activities that need you to be alert.

Casgevy contains sodium, dimethyl sulfoxide (DMSO) and dextran 40

This medicine contains approximately 5.3-70 mg sodium (main component of table salt) per vial. This is equivalent to 0.3-4% of the recommended maximum daily dietary intake of sodium for an adult. The total number of vials comprising a dose varies per patient.

DMSO and dextran 40 are substances used to preserve frozen cells. If you have not previously come into contact with them, the medical team will monitor you closely for any allergic reactions during and after the infusion of Casgevy.

3. How Casgevy is made and given

Casgevy is a once-only treatment. You will not be given Casgevy again.

Casgevy can only be given in an authorised treatment centre (specialised hospital) by doctors with experience in stem cell transplants, and in the treatment of patients with blood disorders such as beta-thalassemia and sickle cell disease.

STEP 1: Before Casgevy treatment, a doctor will give you a **mobilisation medicine**. This medicine moves blood stem cells from your bone marrow into the blood stream. The cells are then collected in a machine that separates the different blood cells (this is called *apheresis*). The entire step may happen more than once. Each time, it takes about one week.

'Rescue cells' are also collected and stored at the hospital. These are your existing blood stem cells and are kept untreated just in case there is a problem in the treatment process. See above in section 2, "*If Casgevy treatment cannot be completed or fails*".

STEP 2: Your blood stem cells will be sent to the manufacturing site where they are **used to make Casgevy**. It may take up to 6 months from the time your cells are collected to manufacture and test Casgevy before it is sent back to your doctor.

STEP 3: Shortly before your stem cell transplant, the doctor will give you a **conditioning medicine** for a few days in hospital. This will prepare you for treatment by clearing cells from the bone marrow, so they can be replaced with the modified cells in Casgevy. After you are given this medicine, your blood cell levels will fall to very low levels. You will stay in the hospital at this point and remain in the hospital until after the Casgevy infusion.

STEP 4: One or more vials of Casgevy will be given into a vein (*intravenous infusion)* over a few hours.

After the Casgevy infusion, you will stay in hospital so that your healthcare team can closely monitor your recovery. The length of time for sufficient recovery can vary. A doctor on the team will decide when you can go home.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Talk to your doctor or nurse about possible side effects.

Some side effects are related to the mobilisation medicine and the conditioning medicine. You should also read the package leaflets for these medicines.

The following serious side effects can happen within the first few days or weeks after treatment but can also develop much later.

- Pain in the right upper abdomen under the ribs, yellowing of eyes or skin, rapid weight gain, swelling of arms, legs and abdomen, and trouble breathing. **These may be signs of a serious liver condition.**
- Severe headache, abnormal bruising, prolonged bleeding, or bleeding without injury such as nosebleeds, bleeding from gums, blood in your urine, stool, or vomit, or coughing up blood. **These may be signs of bleeding** caused by lower levels of platelet cells in your blood, reducing the ability of blood to clot.
- Fever, chills or infections. **These may be signs of lower levels of white bloods cells,** reducing the ability to fight infections.

Tell your doctor immediately if you get any of the side effects listed above.

Other side effects seen with Casgevy:

Very common side effects (may affect more than 1 in 10 people)

- lower levels of white blood cells, sometimes with a fever, which may make you more susceptible to infection
- lower levels of red blood cells
- increased liver enzymes (signs of stress on the liver)
- yellow discolouration of the eyes and skin (*jaundice*), caused by high levels of bilirubin in the blood
- changes in levels of potassium, phosphate and magnesium in your blood
- fever
- headache
- mouth pain
- nosebleed
- inflamed mucous membranes (e.g., gums)
- inflammation of the stomach or colon
- stomach pain
- nausea
- vomiting
- diarrhoea
- constipation
- decreased appetite
- weight loss
- swelling in the face, hands and feet caused by excess fluid
- pain in bones or muscles
- sunspots, freckles or red dots on the skin
- dry or flaky skin
- rash
- hair loss
- feeling tired or weak

Common side effects (may affect up to 1 in 10 people)

- inflammation caused by the immune system making too many infection fighting cells (*haemophagocytic lymphohistiocytosis*) - symptoms may include enlarged liver and/or spleen, skin rash, breathing problems, easy bruising, kidney abnormalities, and heart problems
- difficulty breathing, which could require oxygen to help you breathe, sometimes with pain in the chest, fever, chills or coughing
- multiple symptoms such as fever, skin rash, diarrhoea or unexplained weight gain occurring at the same time, usually in the first month after treatment (*engraftment syndrome*)
- increased time for blood to clot
- infections
- enlarged spleen or liver
- increased heart rate
- decreased blood pressure
- changes in levels of calcium in your blood
- low oxygen levels in the blood
- irregular blood clotting
- chills
- problem with nerves, causing pain, numbness or tingling
- tingling or prickling sensation
- blurred vision
- cough
- sore throat
- trouble swallowing
- indigestion
- bruising or reddening of the skin
- cuts or scrapes of the skin
- itchy skin
- joint pain or general pain
- menstruation changes such as missed menstruation, bleeding between menstruation periods, irregular menstruation, vaginal pain, pain during menstruation, and early menopause.
- difficulty or discomfort when urinating
- weight gain
- dry eyes
- hot flushes

Tell your doctor or nurse right away if side effects become severe.

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:

Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Casgevy

This information is intended for doctors and nurses only.

As this medicine will be given by a qualified doctor or nurse, they are responsible for the correct storage of the medicine before and during its use, as well as for its correct disposal.

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

Do not use this medicine after the expiry date which is stated on the carton and on each vial.

Store frozen, at or below -135 °C for up to two years. Keep the vial(s) in the carton until ready to thaw. Thaw one vial at a time. Do not thaw until ready to infuse. Do not re-freeze after thawing. Once thawed, store at room temperature (20 °C to 25 °C) and infuse within 20 minutes. Refer to the information for healthcare professionals below.

This medicine contains modified human blood cells. Unused medicine must be disposed of in compliance with the local guidelines on handling human-derived material.

6. Contents of the pack and other information

What Casgevy contains
- The active substance is exagamglogene autotemcel. Each mL of Casgevy contains 4-13 × 10^6 $CD34^+$ cells (blood stem cells).
- The other ingredients are a solution used to preserve frozen cells, which contains sodium, dimethyl sulfoxide (DMSO) and dextran 40. See section 2.

What Casgevy looks like and contents of the pack

Casgevy is a semi-transparent dispersion for infusion. Casgevy is supplied in vials containing 1.5 mL to 20 mL. One or more vials are packed in a carton. One carton may contain up to 9 vials. Your dose may consist of multiple vials and cartons.

Your name and date of birth, as well as coded information identifying you as the intended recipient are printed onto each carton and vial.

Marketing Authorisation Holder and Manufacturer

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This leaflet was last revised in November 2023.

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine. The Medicines and Healthcare products Regulatory Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information
Detailed information on this medicine is available on the website of the Medicines and Healthcare products Regulatory Agency: http://www.mhra.gov.uk.

For health professionals only

The following information is intended for healthcare professionals only:

Precautions to be taken before handling or administering the medicinal product
Casgevy is intended solely for autologous use. Do not sample, alter, or irradiate the medicinal product. Irradiation could lead to inactivation of the product.

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.

Receipt and storage of Casgevy

- Casgevy is shipped to the treatment centre in a liquid nitrogen dry shipper.
- 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 at 0800-028-2616.
- Store in the vapour phase of liquid nitrogen at ≤ -135°C until ready for thaw and administration.

Preparation prior to administration

- 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.
- Before thaw, confirm the patient's identity matches the patient information on the Casgevy vial(s). Do not thaw the Casgevy vials 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 at 0800-028-2616.
- 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

Thawing the Casgevy vials

- When the dose consists of multiple vials, thaw and administer one vial at a time. While 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 suspension of cells.
- Infuse within 20 minutes of thaw.

Administration of 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.**

1. Attaching the vial adapter and filter

- Remove the flip-away tab of the vial cap; clean the septum with an alcohol swab.
- Remove the cap on the adapter spike.
- With the thumb and forefinger of both hands, push the adapter into the vial septum, applying equal pressure until you hear a single pop.
- Pull up on the adapter until you feel it lock.
- Attach the filter to the vial adapter.

2. Withdrawal of Casgevy from the vial

- Attach an empty 30 mL syringe to the filter.
- Withdraw the entire vial product volume.
- Remove the product-filled syringe from the filter and set aside.
- Draw 5 to 10 mL of saline into the empty 10 mL syringe.
- Attach the saline-filled syringe to the filter.
- Inject the saline and remove the empty syringe from the filter. Discard the empty syringe.
- Attach the product-filled syringe to the filter.
- Withdraw the contents of the vial into the product syringe, then remove the syringe from the filter.
- The optional product/patient identifier label can be peeled from the lot information sheet and affixed to the syringe.

3. Administration of Casgevy through a central venous catheter

- 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).
- Casgevy is administered as an intravenous bolus.
- The total volume of Casgevy administered within one hour must not exceed 2.6 mL/kg.
- 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.

Repeat the steps listed above for each remaining vial.

Measures to take in case of accidental exposure

In case of accidental exposure local guidelines on handling of human-derived material should be followed. Work surfaces and materials which have potentially been in contact with Casgevy must be decontaminated with appropriate disinfectant.

Precautions to be taken for the disposal of the medicinal product

Unused medicinal product and all material that has been in contact with Casgevy (solid and liquid waste) must be handled and disposed of as potentially infectious waste in accordance with local guidelines on handling of human-derived material.