FILE NAME	UK_Upstaza_PIL_V1
COMPONENT	Leaflet
Date	22-03-24
VERSION	5
DIMENSIONS	480 x 380 mm

BLACK CYAN DIELINE MAGENTA YELLOW PLACEHOLDER

FOOT

GLUE AREA

PANEL TO VIEW

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PANEL TO VIEW

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GLUE AREA

HEAD

Package leaflet: Information for the patient

Upstaza 2.8 × 10^{11} vector genomes/0.5 mL solution for infusion

eladocagene exuparvovec

▼ 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 or your child may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you or your child is given this medicine because it contains important information.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you or your child gets 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 Upstaza is and what it is used for
2. What you need to know before you or your child is given Upstaza
3. How Upstaza is given to you or your child
4. Possible side effects
5. How Upstaza is stored
6. Contents of the pack and other information

1. What Upstaza is and what it is used for

What Upstaza is
Upstaza is a gene therapy medicine that contains the active substance eladocagene exuparvovec.

What Upstaza is used for
Upstaza is used for the treatment of patients aged 18 months and older, with a deficiency of the protein called aromatic L-amino acid decarboxylase (AADC). This protein is essential to make certain substances that the body's nervous system needs to work properly.

AADC deficiency is an inherited condition caused by a mutation (change) in the gene that controls the production of AADC (also called *dopa decarboxylase* or *DDC* gene). The condition prevents development of the child's nervous system, which means that many of the body's functions do not develop correctly during childhood, including movement, eating, breathing, speech and mental ability.

How Upstaza works
The active substance in Upstaza, eladocagene exuparvovec, is a type of virus called adeno-associated virus that has been modified to include a copy of the *DDC* gene that works correctly. Upstaza is given by infusion (drip) into an area of the brain called the putamen, where AADC is made. The adeno-associated virus allows the *DDC* gene to pass into brain cells. In this way, Upstaza enables the cells to produce AADC so that the body can then make the substances that the nervous system needs.

The adeno-associated virus used to deliver the gene does not cause disease in humans.

2. What you need to know before you or your child is given Upstaza

You or your child will not be given Upstaza:
- if you or your child is allergic to eladocagene exuparvovec or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
- Mild or moderate uncontrollable jerky movements (also called dyskinesia) or sleep disorders (insomnia) may occur or worsen 1 month after treatment with Upstaza and last for several months after. Your doctor will decide if you or your child needs treatment for these effects.
- The doctor will monitor you or your child for complications of Upstaza treatment, such as leakage of the fluid surrounding the brain, meningitis, or encephalitis.
- Within the next days following the surgery, the doctor will monitor you or your child for any complications secondary to the surgery, the disease, and to the general anaesthesia. Some of the disease symptoms may be amplified during that period.
- Some specific symptoms of AADC deficiency may persist after treatment, examples of such symptoms may include impact on mood, sweating, and body temperature.
- After treatment, some medicine may enter your or your child's body fluids (eg, tears, blood, nasal secretions, and cerebrospinal fluid); this is known as 'shedding'. You or your child and the child's caregiver (especially if pregnant, breast-feeding, or with a suppressed immune system) should wear gloves and place any used dressings and other waste material with tears and nasal secretions in sealed bags before throwing them away. You should follow these precautions for 14 days.
- You or your child must not donate blood, organs, tissues, and cells for transplantation after treatment with Upstaza. This is because Upstaza is a gene therapy product.

Children and adolescents
Upstaza **has not** been studied in children under 18 months of age. Limited experience is available in children above 12 years.

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

Your doctor will confirm if you or your child can receive vaccinations as normal or if adjustments to the schedule are required.

Pregnancy and breast-feeding and fertility

The effects of this medicine on pregnancy and the unborn child are not known.

Upstaza has not been studied in breast-feeding women.

There is no information on the effect of Upstaza on male or female fertility.

Upstaza contains sodium and potassium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

This medicine contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially 'potassium-free'.

3. How Upstaza is given to you or your child

- Upstaza will be given to you or your child in an operating room by neurosurgeons experienced in brain surgery.
- Upstaza is given under anaesthetic. The neurosurgeon will talk to you about the anaesthesia and how it will be given.
- Before giving Upstaza, the neurosurgeon will make two small holes in you or your child's skull, one on each side.
- Upstaza will then be infused through these holes into four sites in your or your child's brain, in an area called the putamen.
- After the infusion, the two holes will be closed, and you or your child will have a brain scan.
- You or your child will need to stay in or near the hospital for a few days to monitor recovery and check for any side effects from the surgery or the anaesthesia.
- The doctor will see you or your child in the hospital twice, once around 1 week after the surgery, and then 3 weeks after the surgery, to continue following up on recovery and to check for any side effects from the surgery and treatment.

If you or your child is given more Upstaza than should be
As this medicine is given to you or your child by a doctor, it is unlikely that you or your child will be given too much. If it does occur, your doctor will treat the symptoms, as necessary.

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 following side effects may happen with Upstaza:

Very common (may affect more than 1 in 10 people)
- Insomnia (difficulty sleeping)
- Dyskinesia (Uncontrollable jerky movements)

Common (may affect up to 1 in 10 people)
- Feeding difficulties
- Irritability
- Increased saliva production

The following side effects may happen with the surgery to administer Upstaza:

Very common (may affect more than 1 in 10 people)
- Low levels of red blood cells (anaemia)
- Leakage of the fluid surrounding the brain (called cerebrospinal fluid) (possible symptoms include headache, nausea and vomiting, neck pain or stiffness, change in hearing, sense of imbalance, dizziness or vertigo)

The following side effects may happen within the next 2 weeks following the surgery to administer Upstaza, due to either anaesthesia or to post-surgery effects:

Very common (may affect more than 1 in 10 people)
- Pneumonia
- Low level of blood potassium
- Irritability
- Hypotension (low blood pressure)
- Gastrointestinal bleeding, diarrhoea
- Pressure sore
- Fever
- Abnormal breath sounds

Common (may affect up to 1 in 10 people)
- Gastroenteritis
- Dyskinesia (Uncontrollable jerky movements)
- Cyanosis (bluish discolouration of the skin caused by lack of oxygen in the blood)
- Hypovolemic shock (severe loss of blood or body fluids)
- Respiratory failure
- Mouth ulceration
- Diaper rash, rash
- Hypothermia (low body temperature)
- Tooth extraction

Reporting of side effects
If you or your child gets 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:

United Kingdom (Great Britain)
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 Upstaza is stored

The following information is intended for doctors only.

Upstaza will be stored at the hospital. It has to be stored and transported frozen at ≤ -65 °C. It is thawed before use and, once thawed, has to be used within 6 hours. It should not be re-frozen. Do not use this medicine after the expiry date, which is stated on the carton after EXP.

6. Contents of the pack and other information

What Upstaza contains
- The active substance is eladocagene exuparvovec. Each 0.5 ml of solution contains 2.8 × 10^{11} vector genomes of eladocagene exuparvovec.

The other ingredients are potassium chloride, sodium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate, poloxamer 188, water for injections (see section 2 "Upstaza contains sodium and potassium").

What Upstaza looks like and contents of the pack

Upstaza is a clear to slightly opaque, colourless to faint-white solution for infusion, supplied in a clear glass vial.

Each carton contains 1 vial.

Marketing Authorisation Holder
PTC Therapeutics International Limited
70 Sir John Rogerson's Quay
Dublin 2
Ireland

Manufacturer
Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk, Co. Louth, A91 P9KD
Ireland

This leaflet was last revised in 11/2022.

This medicine has been authorised under 'exceptional circumstances'. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. The Medicines and Healthcare products Regulatory Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the Medicines and Healthcare products Regulatory Agency (MHRA) website: www.mhra.gov.uk

The following information is intended for healthcare professionals only:

Instructions on preparation, administration, measures to take in case of accidental exposure, and disposal of Upstaza

Each vial is for single use only. This medicinal product should only be infused with the SmartFlow ventricular cannula.

Precautions to be taken before handling or administering the medicinal product

This medicinal product contains genetically modified virus. During preparation, administration, and disposal, personal protective equipment (including gown, safety glasses, mask, and gloves) should be worn when handling eladocagene exuparvovec and materials that have been in contact with the solution (solid and liquid waste).

Thawing in the hospital pharmacy

- Upstaza is delivered to the pharmacy frozen and must be maintained in the outer carton at ≤ 65 ºC until prepared for use.
- Upstaza should be handled aseptically under sterile conditions.
- Allow the frozen vial of Upstaza to thaw upright at room temperature until the content is completely thawed. Gently invert the vial approximately 3 times; do NOT shake.
- Inspect Upstaza after mixing. If particulates, cloudiness, or discolouration are visible, do not use the product.

Preparation prior to administration

- Transfer the vial, syringe, needle, syringe cap, sterile bags, or sterile wrappings compliant with hospital procedure for transfer and use of the filled syringe in the planned surgical suite, and label into the Biological Safety Cabinet (BSC). Wear sterile gloves and other personal protective equipment (including gown, safety glasses and mask) as per normal procedure for BSC work.
- Open the 1 mL or 5 mL syringe [1 mL or 5 mL, polypropylene syringes with latex-free elastomer plunger, lubricated with medical-grade silicone oil] and label as the product-filled syringe per pharmacy procedure and local regulations.
- Attach the 18- or 19-gauge filter needle [18- or 19-gauge, 1.5-inch, stainless steel, 5-µm filter needles] to the syringe.
- Draw the full volume of the vial of Upstaza into the syringe. Invert the vial and syringe and partially withdraw or angle the needle as necessary to maximise recovery of product.
- Draw air in the syringe so that the needle is emptied of product. Carefully remove the needle from 1 mL or 5 mL syringe containing Upstaza. Purge the air from the syringe until there is no air bubble and then cap with a syringe cap.
- Wrap the syringe in one sterile plastic bag (or several bags based on standard hospital procedure) and place in an appropriate secondary container (eg, hard plastic cooler) for delivery to the surgical suite at room temperature. Use of the syringe (ie, connecting the syringe to the syringe pump and starting priming of the cannula) should begin within 6 hours of starting product thaw.

Administration in the surgical suite

- Tightly connect the syringe containing Upstaza to the SmartFlow ventricular cannula.
- Install the Upstaza syringe into a syringe infusion pump compatible with the 1 mL or 5 mL syringe. Pump Upstaza with the infusion pump at 0.003 mL/min until the first drop of Upstaza can be seen from the tip of the needle. Stop and wait until ready for infusion.

Precautions to be taken for the disposal of the medicinal product and accidental exposure

- Accidental exposure to eladocagene exuparvovec, including contact with skin, eyes, and mucous membranes, is to be avoided.
- In the event of exposure to skin, the affected area must be thoroughly cleaned with soap and water for at least 5 minutes. In the event of exposure to eyes, the affected area must be thoroughly flushed with water for at least 5 minutes.
- In the event of needlestick injury, the affected area must be cleaned thoroughly with soap and water and/or a disinfectant.
- Any unused eladocagene exuparvovec or waste material should be disposed of in compliance with local guidance for pharmaceutical waste. Potential spills should be wiped with absorbent gauze and disinfected using a bleach solution followed by alcohol wipes.
- After administration, the risk of shedding is considered to be low. It is recommended that caregivers and patient families are advised on and follow proper handling precautions of patient bodily fluids and waste for 14 days after administration of eladocagene exuparvovec (see SmPC section 4.4).

Posology

Treatment should be administered in a centre which is specialised in stereotactic neurosurgery, by a qualified neurosurgeon under controlled aseptic conditions.

Patients will receive a total dose of 1.8 × 10^{11} vg delivered as four 0.08-mL (0.45 × 10^{11} vg) infusions (two per putamen).
The posology is the same for the entire population covered by the indication.

Method of administration

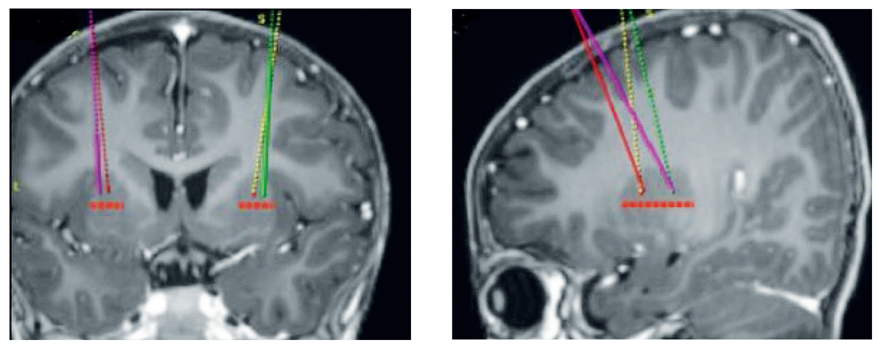
Intraputaminal use.

Upstaza administration may cause cerebrospinal fluid leak post-surgery. Patients undergoing Upstaza treatment should be carefully monitored after administration.

Neurosurgical administration
Upstaza is a single-use vial administered by bilateral intraputaminal infusion in one surgical session at two sites per putamen. Four separate infusions of equal volumes are performed to the right anterior putamen, right posterior putamen, left anterior putamen, and left posterior putamen.

Follow the steps below to administer Upstaza:
- The target infusion sites are defined per standard stereotactic neurosurgical practice. Upstaza is administered as a bilateral infusion (2 infusions per putamen) with an intracranial cannula. The final 4 targets for each trajectory should be defined as 2 mm dorsal to (above) the anterior and posterior target points in the mid-horizonal plane (Figure 1).

Figure 1 Four target points for infusion sites



- After stereotactic registration is complete, the entry point on the skull should be marked. Surgical access through the skull bone and dura should be performed.
- The infusion cannula is placed at the designation point in the putamen using stereotactic tools based on the trajectories planned. Of note, the infusion cannula is placed and infusion performed separately for each putamen.
- Upstaza is infused at a rate of 0.003 mL/min at each of the 2 target points in each putamen; 0.08 mL of Upstaza is infused per putaminal site resulting in 4 infusions with a total volume of 0.320 mL (or 1.8 × 10^{11} vg).
- Starting with the first target site, the cannula is inserted through a burr hole into the putamen and then slowly withdrawn, distributing the 0.08 mL of Upstaza across the planned trajectory to optimise distribution across the putamen.
- After the first infusion, the cannula is withdrawn and then re-inserted at the next target point, repeating the same procedure for the other 3 target points (anterior and posterior of each putamen).
- After standard neurosurgical closure procedures, the patient then undergoes a postoperative brain imaging (magnetic resonance imaging [MRI] or computerised tomography [CT]) to ensure there are no complications (ie, bleeding).
- The patient must reside within the vicinity of the hospital where the procedure was performed for a minimum of 48 hours following the procedure. The patient may return home, post-procedure, based on treating physician's advice. The post-treatment care should be managed by the referring neurosurgeon and the referring neurologist. The patient should have a follow-up 7 days after surgery to ensure that no complications have developed. A second follow-up visit should take place 2 weeks later (ie, 3 weeks after the surgery) to monitor post-surgical recovery and occurrence of adverse events.
- Patients will be offered to enrol in a registry in order to further evaluate the long-term safety and effectiveness of the treatment under normal conditions of clinical practice.

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