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

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Eladocagene exuparvovec is a gene therapy medicinal product that expresses the human aromatic L-amino acid decarboxylase enzyme (hAADC). It is a non-replicating recombinant adeno-associated virus serotype 2 (AAV2) based vector containing the cDNA of the human dopa decarboxylase (DDC) gene under the control of the cytomegalovirus immediate-early promoter.

Eladocagene exuparvovec is produced in human embryonic kidney cells by recombinant DNA technology.

2.2 Qualitative and quantitative composition

Each single-dose vial contains 2.8×10^{11} vg of eladocagene exuparvovec in 0.5 extractable mL of solution. Each mL of solution contains 5.6×10^{11} vg of eladocagene exuparvovec.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Following thaw from frozen, the solution for infusion is a clear to slightly opaque, colourless to faint-white liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Upstaza is indicated for the treatment of patients aged 18 months and older with a clinical, molecular, and genetically confirmed diagnosis of aromatic L-amino acid decarboxylase (AADC) deficiency with a severe phenotype (see section 5.1).

4.2 Posology and method of administration

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

Posology

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.

Special populations

Paediatric population
The safety and efficacy of eladocagene exuparvovec in children aged below 18 months have not yet been established. No data are available.
There is limited experience in patients aged 12 years and older. The safety and efficacy of eladocagene exuparvovec in these patients have not been established. Currently available data are described in section 5.1. No dose adjustment should be considered.

Hepatic and renal impairment
The safety and efficacy of eladocagene exuparvovec in patients with hepatic and renal impairment have not been evaluated.

Immunogenicity
There is no safety or efficacy data for patients whose pre-treatment neutralising antibody levels to AAV2 was > 1:20 (see section 4.4).

Method of administration

Intraputaminal use.

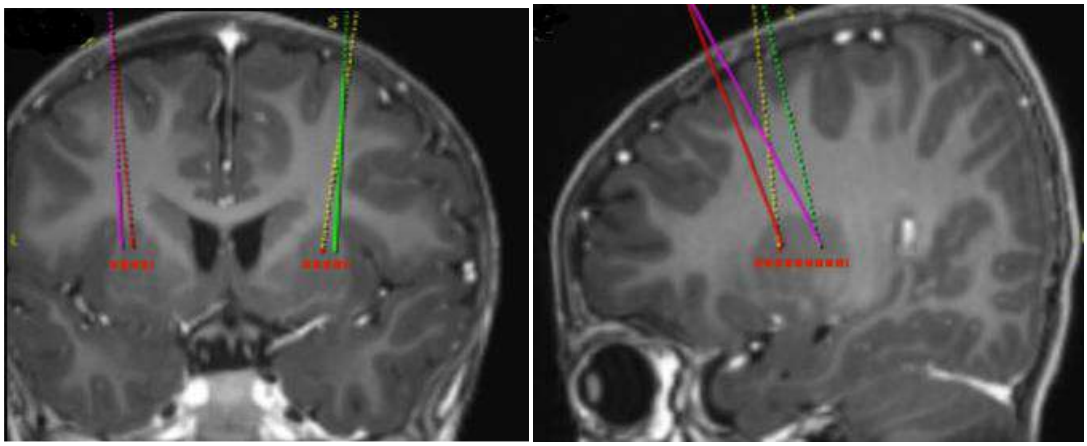
Preparation
Upstaza is a sterile solution for infusion that requires thawing and preparation by the hospital pharmacy prior to administration.

For detailed instructions on preparation, administration, measures to take in case of accidental exposure and disposal of Upstaza, see section 6.6.

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.
For instructions on preparation of the surgical suite infusion of Upstaza, see section 6.6.

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 computerised tomography imaging examination 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 paediatric neurologist and with the neurosurgeon. 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Proper aseptic techniques should always be used for the preparation and infusion of Upstaza.

Monitoring

Patients undergoing gene therapy should be closely monitored for procedure-related complications, complications related to their underlying disease, and risks associated with general anaesthesia during the peri-operative period. Patients may experience exacerbations of symptoms of their underlying AADC deficiency as a result of surgery and anaesthesia (see section 4.8).

Autonomic and serotonergic symptoms of AADC may persist after treatment with eladocagene exuparvovec.

Traceability

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

Immunogenicity

Experience with eladocagene exuparvovec in patients with anti-AAV2 antibody levels > 1:20 prior to treatment is not available.

Cerebrospinal fluid leaks

Cerebrospinal fluid (CSF) leaks occur when there is a tear or hole in the meninges surrounding the brain or spinal cord, allowing the CSF to escape. Upstaza is administered by bilateral intraputaminal infusion using burr holes, therefore, CSF leak may occur postoperatively. Patients undergoing eladocagene exuparvovec treatment should be carefully monitored after administration for CSF leaks, particularly in relation to the risk of meningitis and encephalitis.

Dyskinesia

AADC-deficient patients may have increased sensitivity to dopamine due to their chronic dopamine deficiency. After treatment with eladocagene exuparvovec, increase in dyskinesia have been reported in 24/28 patients (see section 4.8). The increase of dyskinesia due to this dopamine sensitivity generally starts 1 month after the administration of gene therapy and gradually decreases over several months. The use of dopamine antagonists (risperidone) may be considered to control dyskinesia symptoms (see section 5.1).

Risk of shedding

The risk of shedding is considered to be low due to very limited systemic distribution of eladocagene exuparvovec (see section 5.2). As a precautionary measure, patients/caregivers should be advised to handle waste material generated from dressings and/or any secretions (tears, blood, nasal secretions, and CSF) appropriately, which may include storage of waste material in sealed bags prior to disposal and patients/caregivers wearing gloves for dressing changes and waste disposal. These handling precautions should be followed for 14 days after administration of eladocagene exuparvovec. It is recommended that patients/caregivers wear gloves for dressing changes and waste disposal, especially in case of pregnancy, breast-feeding, or immunodeficiency of caregivers.

Blood, organ, tissue, and cell donation

Patients treated with Upstaza must not donate blood, organs, tissues, and cells for transplantation.

Sodium and potassium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.
This medicinal product contains less than 1 mmol potassium (39 mg) per dose, that is to say essentially ‘potassium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. No interaction is expected due to very limited systemic distribution of eladocagene exuparvovec.

Vaccinations

Vaccination schedule should proceed as normal.

4.6 Fertility, pregnancy and lactation

Based on the lack of systemic exposure and negligible biodistribution to the gonads, the risk for germline transmission is low.

Pregnancy

There are no data from the use of eladocagene exuparvovec in pregnant women. Animal reproductive studies have not been conducted with eladocagene exuparvovec (see section 5.3).

Breast-feeding

It is unknown whether eladocagene exuparvovec is excreted in human milk.
Eladocagene exuparvovec is not absorbed systemically following intraputaminal administration, and no effect on the breastfed newborns/infants are anticipated.

Fertility

There are no clinical or nonclinical data available regarding the effect of eladocagene exuparvovec on fertility.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile

The safety information was observed in 3 open-label clinical studies in which eladocagene exuparvovec was administered to 28 AADC-deficient patients aged 19 months to 8.5 years at the time of dosing. Patients were followed for a median duration of 52.3 months (minimum of 3.1 months to a maximum of 9.63 years). The most common adverse reaction was dyskinesia; it was reported in 24 (85.7%) patients and was prevalent during the first 2 months post-treatment.

Tabulated list of adverse reactions

The adverse reactions are reported in Table 1. The adverse reactions are listed by system organ class and frequency using the following convention: 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 1 Adverse reactions occurring in ≥ 2 patients in 3 open-label clinical studies (n = 28)

System organ class	Very common	Common
Psychiatric disorders	Initial insomnia, irritability	
Nervous system disorders	Dyskinesia	
Gastrointestinal disorders		Salivary hypersecretion

Table 2 **Neurosurgery-related adverse reactions occurring in ≥ 2 patients in 3 open-label clinical studies (n=28)**

Adverse reaction category	Very common
Blood and lymphatic system disorders	Anaemia
Nervous system disorders	Cerebrospinal fluid leakage[a]

[a] May include pseudomeningocele

Table 3 **Anaesthesia and postoperative related adverse reactions in ≥ 2 patients within ≤ 2 weeks after administration, in 3 open label clinical studies (n=28)**

Adverse reaction category	Very common	Common
Infections and infestations	Pneumonia	Gastroenteritis
Metabolism and nutrition disorders	Hypokalaemia	
Psychiatric disorders	Irritability	
Nervous system disorders		Dyskinesia
Cardiac disorders		Cyanosis
Vascular disorders	Hypotension	Hypovolemic shock
Respiratory, thoracic and mediastinal disorders		Respiratory failure
Gastrointestinal disorders	Upper gastrointestinal haemorrhage, Diarrhoea	Mouth ulceration
Skin and subcutaneous tissue disorders		Decubitus ulcer, Dermatitis diaper, Rash
General disorders and administration site conditions	Pyrexia Breath sounds abnormal	Hypothermia
Surgical and medical procedure		Tooth extraction

Description of selected adverse reactions

Dyskinesia
Events of dyskinesia were reported in 24 (85.7%) subjects (see section 4.4).
Of the 35 events of dyskinesia, 33 events were mild to moderate and 2 were severe. The majority of events resolved in approximately 2 months and all resolved within 7 months. The mean time to onset of events of dyskinesia was 25.8 days after receiving gene therapy. Events of dyskinesia were managed with routine medical care, such as anti-dopaminergic treatment.

Immunogenicity
Titres of anti-AAV2 antibodies were measured pre- and post-gene therapy in the clinical studies. All patients that received eladocagene exuparvovec had anti-AAV2 titres at or below 1:20 before treatment. Following treatment, most subjects (n = 18) were positive for anti-AAV2 antibodies at least once within the first 12 months. In general, antibody levels stabilised or declined with time. There was no specific follow up program to capture potential immunogenicity reactions in any of the clinical studies, but presence of anti-AAV2 antibodies in the clinical studies was not reported to be associated with increase in severity, number of adverse reactions, or with decreased efficacy.
Experience with eladocagene exuparvovec in patients with anti-AAV2 antibody levels > 1:20 prior to treatment is not available.
The immune response to the transgene and the cellular immune response were not measured.

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

There is no clinical experience with overdose of eladocagene exuparvovec. Symptomatic and supportive treatment, as deemed necessary by the treating physician, is advised in case of overdose. Close clinical observation and monitoring of laboratory parameters (including complete blood count with differential, and comprehensive metabolic panel) for systemic immune response are recommended. For instructions in case of accidental exposure, see section 6.6.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other alimentary tract and metabolism products, Enzymes; ATC code: A16AB26

Mechanism of action

AADC deficiency is an inborn error of neurotransmitter biosynthesis with an autosomal recessive inheritance in the dopa decarboxylase (*DDC*) gene. The *DDC* gene encodes the AADC enzyme, which converts L-3,4-dihydroxyphenylalanine (L-DOPA) to dopamine. Mutations in the *DDC* gene result in reduction or absence of AADC enzyme activity, causing a reduction in the levels of dopamine and the failure of most patients with AADC deficiency to achieve developmental milestones.

Eladocagene exuparvovec is a gene therapy based on recombinant AAV2 vector containing the human cDNA for the *DDC* gene. After infusion into the putamen, the product results in the expression of the AADC enzyme and subsequent production of dopamine, and consequently, development of motor function in treated AADC-deficient patients.

Pharmacodynamic effects

L-6-[^{18}F] fluoro-3, 4-dihydroxyphenylalanine (^{18}F-DOPA) uptake in central nervous system (CNS)
Measurement of ^{18}F-DOPA uptake in the putamen via positron emission tomography (PET) imaging following treatment is an objective measurement of de novo dopamine production in the brain and assesses the success and stability of the AADC gene transduction over time. Most patients demonstrated small sustained increases in PET-specific uptake. An increase was evident as early as 6 months, was further increased by 12 months after treatment, and sustained at least for 5 years.

Table 4 PET specific uptake after eladocagene exuparvovec treatment (Studies AADC-010, AADC-011)

Timepoint	Baseline (n=20)	Change from baseline Month 12 (n=17)	Change from baseline Month 24 (n=15)	Change from baseline Month 60 (n=4)
PET specific uptake	0.27	0.32	0.36	0.39

Clinical efficacy and safety

The efficacy of Upstaza gene therapy was assessed in 2 clinical studies (AADC-010, AADC-011). Together, these 2 studies included 20 patients with severe AADC deficiency, diagnosed by decreased homovanillic acid and 5-hydroxyindoleacetic acid and elevated L-DOPA CSF levels, the presence of *DDC* gene mutation in both alleles, and the presence of clinical symptoms of AADC deficiency (including developmental delay, hypotonia, dystonia, and oculogyric crisis [OGC]). These patients had not achieved motor development milestones at baseline including the ability to sit, stand or walk, compatible with the severe phenotype. Patients were treated with a total dose of 1.8×10^{11} vg (N = 13)

or 2.4×10^{11} vg (N = 7) during a single operative session. The results for efficacy and safety parameters were similar between the 2 doses.
Study AADC-CU/1601 was conducted with treatment from an older manufacturing process. This study enrolled 8 subjects and demonstrated similar results with benefits maintained up to 60 months.

Motor function
Motor milestone achievement was derived from the Peabody Developmental Motor Scale, version 2 (PDMS-2). The PDMS-2 is an assessment of a child's motor development up to the developmental age of 5, and assesses both gross and fine motor skills, and with items that specifically capture motor milestone achievement. The PDMS-2 motor skill items were chosen to determine the number of patients who achieved at least the following motor milestones: 1) full head control, 2) sitting unassisted, 3) standing with support, and 4) walking assisted.
Table 5 summarises patient motor milestone achievement at specific timepoints during the first 60 months following treatment administration and cumulatively throughout the entire clinical programme. The primary efficacy endpoint was assessed at 24 months after gene therapy. Not all subjects reached the timepoints specified in the Table 5 at the time of data cut.
Treatment with eladocagene exuparvovec demonstrated acquisition of motor milestones observed as early as 12 months post-surgery. Key motor milestone acquisition was continued or maintained beyond 24 months and up to 60 months.

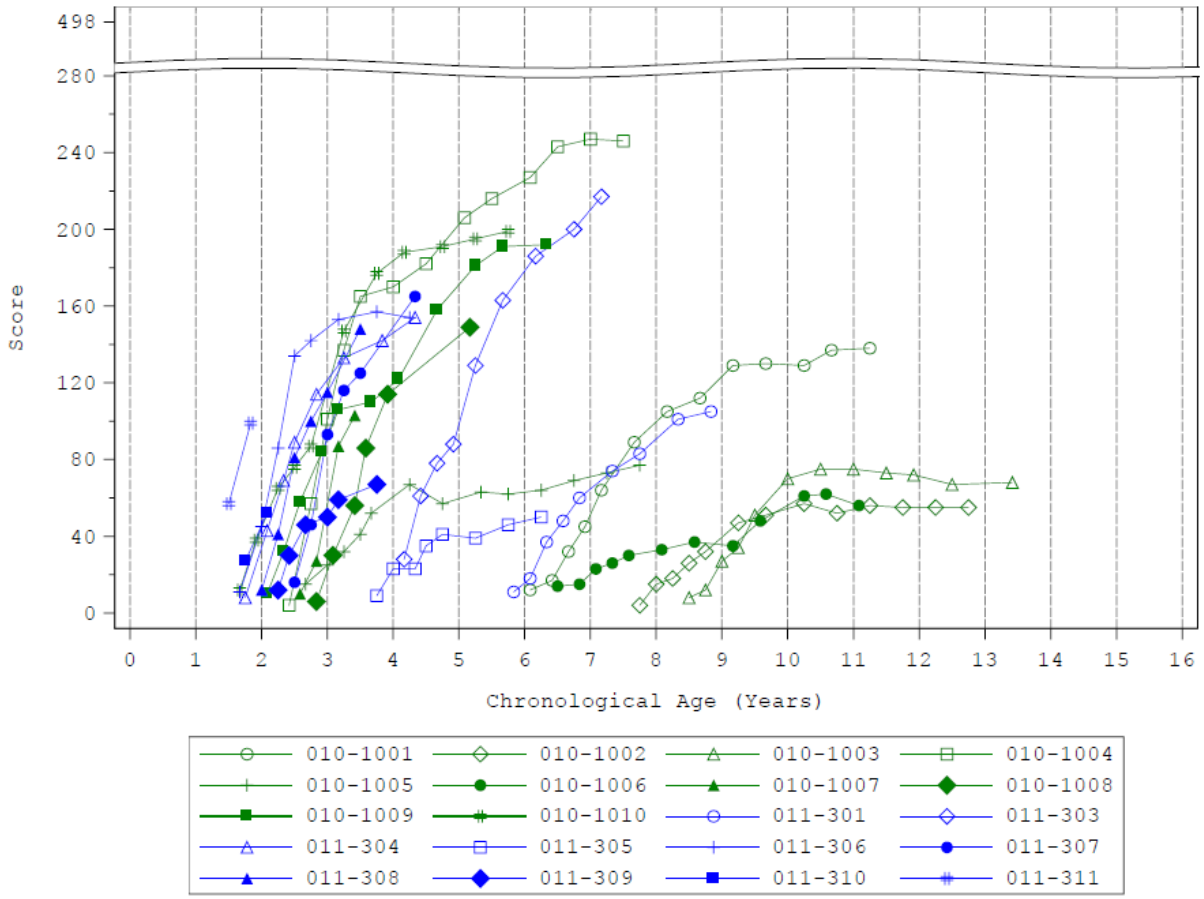
Table 5 Number of patients achieving new PDMS-2 motor milestones (mastery of the skill – score 2) after eladocagene exuparvovec treatment (Studies AADC-010, AADC-011)

	Baseline	**Time interval post-treatment (months)**						**Overall (cumulative) post-treatment**
Motor milestone	**Pre-treatment N = 20**	**0 to 3 N = 20**	**3 to 12 N = 17**	**12 to 24 N = 17**	**24 to 36 N = 13**	**36 to 48 N = 8**	**48 to 60 N = 6**	**60 months N = 20**
Head control	0	1	5	6	2	0	0	14 (70%)
Sitting unassisted	0	1	2	6	2	1	1	13 (65%)
Standing with support	0	0	0	4	1	1	0	6 (30%)
Walking with support	0	0	0	0	2	0	0	2 (10%)

Note: Cumulative column includes all subjects who achieved that particular milestone at any point during the clinical study up to 60 months; Patients needed to reach the score of 2 (indicative of mastery of the skill) on a milestone item to be rated as having achieved that milestone.

PDMS-2 total score
PDMS-2 total score was measured as a secondary endpoint throughout the clinical studies. PDMS-2 maximal scores are 450-482, depending on age (<12 months or > 12 months). All subjects treated with eladocagene exuparvovec showed increases from baseline in mean PDMS-2 total scores over time, with some benefit observed as early as 3 months (Figure 2). At the 24-month timepoint, the least squares (LS) mean of change from baseline in PDMS-2 total score was 104.4 points. Improvement from baseline in PDMS-2 total score was as early as 12 months after treatment (76.1 points) and was maintained to 60 months (108.2 points). Patients who receive eladocagene exuparvovec at a younger age demonstrate a faster treatment response and appear to reach a higher final level.

Figure 2 **Mean PDMS-2 total scores by visit – through month 60 (Studies AADC-010, AADC-011)**



The following data were collected as secondary endpoints in the clinical studies.

Cognitive and communication skills
The total language score, subscales of Bayley-III, a standard assessment of cognition, language, and motor development for, infants and toddlers (1-42 months of age) was assessed in Studies AADC-10 and AADC-11. Over time, all subjects showed gradual and sustained increases in mean total language score, which is the combined score for receptive and expressive communication subscales. The total score of the language subscale is 97. The mean at baseline was 17.70 (N=20). The mean change from baseline for total language score was 7.35 at Month 12 (N = 17), 9.87 at Month 24 (N = 15), and 12.60 at Month 36 (N = 10).

Body weight
Sixteen out of 17 subjects (94%) maintained (47%, 8 subjects) or increased (47%, 8 subjects) their body weight over a 12-month period based on gender and age specific growth chart.

Floppiness (hypotonia) limb dystonia, stimulus-provoked dystonia
Following gene therapy, the percentage of subjects with symptoms of floppiness (hypotonia) decreased from 77.8% at baseline (N=20) to 46.7% at Month 12 (N = 17). No subject experienced limb dystonia and stimulus-provoked dystonia 12 months post-treatment, compared with 66.7% and 11.1% subjects at baseline (N = 20), respectively.

OGC episodes
Following gene therapy, the duration of OGC episodes, was reduced and sustained over time and up to 12 months after treatment. The mean time in OGC was 12.30 hours/week at baseline. This time was reduced following treatment by 1.85 hours per week by Month 3 (N=16) and by 3.66 hours per week by Month 12 (N=6).

The magnitude of the effect of eladocagene exuparvovec on the autonomic symptoms of the AADC deficiency has not been systematically evaluated.

Exceptional circumstances

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

No pharmacokinetic studies with eladocagene exuparvovec have been conducted. Eladocagene exuparvovec is infused directly into the brain and has not been shown to distribute outside the CNS.

Distribution

The biodistribution of the AAV2-hAADC viral vector in blood and urine was measured in subjects using a validated real-time quantitative polymerase chain reaction assay. Subjects treated with Upstaza showed no evidence of detectable viral vector in blood or urine at baseline or through 12 months after treatment.

5.3 Preclinical safety data

No animal studies have been conducted to evaluate the effects of eladocagene exuparvovec on carcinogenesis, mutagenesis and impairment of fertility. In animal studies, no toxicological effects on male or female reproductive organs were observed.

No toxicity was shown in rats up to 6 months following bilateral infusion into the putamen at doses 21 times higher than the human therapeutic dose on a vg per unit of brain weight (g) basis.
Studies in rats showed no viral shedding in blood or any systemic tissues outside of the CNS compartment except for CSF at day 7 where it was positive (copies/µg DNA) in the 6-month toxicology study. When tested at subsequent time points (day 30, day 90 and day 180) all samples were negative.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Potassium chloride
Sodium chloride
Potassium dihydrogen phosphate
Disodium hydrogen phosphate
Poloxamer 188
Water for injections

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 frozen vial

45 months

After thawing and opening

Once thawed, the medicinal product should not be re-frozen.
The filled syringe prepared under aseptic conditions for delivery to the surgical site should be used immediately; if not used immediately, it can be stored at room temperature (below 25°C) and used within 6 hours of starting product thaw.

6.4 Special precautions for storage

Store and transport frozen at ≤ -65° C.
Keep the vial in the outer carton.
For storage conditions after thawing and opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I borosilicate glass vial, with a siliconised chlorobutyl stopper with coating sealed with an aluminium/plastic cap.

Pack size of one vial.

6.6 Special precautions for disposal and other handling

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 5-mL syringe [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 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 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 section 4.4).

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1653/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 July 2022

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER(S) 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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

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

Name and address of the manufacturer of the biological active substance

MassBiologics South Coast
1240 Innovation Way
Fall River
MA 02720
United States

Name and address of the manufacturer responsible for batch release

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

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 market 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 Upstaza in each Member State, the MAH must agree about the content and format of the educational material (ie, Surgical Guide and Pharmacy manual), including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH should ensure that Upstaza is distributed to selected treatment centres performing the administration of the product where qualified staff will have been delivered with educational materials, including the Upstaza Surgical Guide and the Pharmacy manual.

The treatment centres will be selected based on the following criteria:

- Presence of or affiliation with a neurosurgeon experienced in stereotactic neurosurgeries and capable of administrating Upstaza;
- Presence of a clinical pharmacy capable of handling and preparing adeno-associated virus vector-based gene therapy products;
- Ultra-low temperature freezers (≤ -65 ºC) available within the treatment centre pharmacy for treatment storage.

Training and instructions for safe handling and disposal of affected materials for 14 days following product administration should also be provided along with information regarding exclusion from donation of blood, organs, tissues, and cells for transplantation after Upstaza administration.

The qualified staff (ie, neurologists, neurosurgeons, and pharmacists) at the treatment centres should be provided with educational materials including:

- Approved Summary of Product Characteristics.
- Surgical education for Upstaza administration, including description of required equipment, and materials and procedures needed to perform stereotactic administration of Upstaza. The Upstaza Surgical Guide aims at ensuring correct use of the product in order to minimise the risks associated with the administration procedure including cerebrospinal fluid leak.
- Pharmacy education including information on Upstaza receipt, storage, dispensing, preparation, return and/or destruction, and accountability of product.

Prior to scheduling the procedure, a PTC Therapeutics representative will review the Upstaza Surgical Guide with the neurosurgeon and the Pharmacy manual with the pharmacist.

Patients and their caregivers should be provided with the following materials, including:

- Patient Information Leaflet, which should also be available in alternative formats (including large print and as audio file).
- A patient alert card to
  - Highlight the precautionary measures to minimise the risk of shedding.
  - Highlight importance of follow-up visits and reporting side effects to the patient's physician.
  - Inform healthcare professionals that the patient has received gene therapy, and the importance of reporting adverse events.
  - Provide contact information for adverse event reporting.

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

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

Description	Due date
Quality In order to further assess process consistency and maintain patient's safety, the Applicant shall provide the results of the next active substance and next finished product concurrent process validation batches, including hold time data for the finished product batch. This data should be provided by 30 June 2023.	30 June 2023

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Study AADC-1602 (Follow-up of clinical trials): In order to further characterise the long-term efficacy and safety of Upstaza in patients with aromatic L amino acid decarboxylase (AADC) deficiency and with a severe phenotype, the MAH shall submit the results of study AADC-1602, a 10-year follow-up of the patient population enrolled in the clinical studies AADC-CU/1601, AADC-010 and AADC-011.	Annual submission at each annual renewal Final report: 30 June 2030
Study PTC-AADC-MA-406 (Registry-based study) In order to further characterise the long-term efficacy and safety of Upstaza in patients with aromatic L amino acid decarboxylase (AADC) deficiency and with a severe phenotype, the MAH shall conduct and submit the results of study PTC-AADC-MA-406, an observational, multicentre and longitudinal study of patients treated globally with the commercial product, based on data from a registry, according to an agreed protocol.	Annual submission at each annual renewal

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 0.5 mL of solution contains 2.8×10^{11} vector genomes of eladocagene exuparvovec

3. LIST OF EXCIPIENTS

Excipients: potassium chloride, sodium chloride, potassium dihydrogen phosphate, disodium hydrogen phosphate, poloxamer 188, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single administration by bilateral intraputaminal infusion at two sites per putamen.
Read the package leaflet before use.
Intraputaminal use.

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

For single-use only.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store and transport frozen at ≤ -65 ºC.
Keep the vial in the outer carton.
After thawing, use vial within 6 hours. Do not re-freeze.

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

Discard unused product.
This medicine contains genetically modified virus.
Dispose of in compliance with local guidance for pharmaceutical waste.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1653/001

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

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

Upstaza 2.8×10^{11} vg/0.5 mL solution for infusion
eladocagene exuparvovec
Intraputaminal use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 mL

6. OTHER

B. PACKAGE LEAFLET

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

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.

You or your child can receive routine childhood vaccinations as normal.

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)
- Dyskinesia (Uncontrollable jerky movements)
- Insomnia (difficulty sleeping), irritability

Common (may affect up to 1 in 10 people)
- 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)
- Gastrointestinal bleeding, diarrhoea
- Fever, abnormal breath sounds
- Pneumonia
- Low level of blood potassium
- Irritability
- Hypotension (low blood pressure)

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

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 listed in Appendix V. 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 ºC. 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

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

AT, BE, BG, CY, CZ, DK, DE, EE, EL, ES, HR, HU, IE, IS, IT, LT, LU, LV, MT, NL, NO, PL, PT, RO, SI, SK, FI, SE, UK (NI)
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medinfo@ptcbio.com

This leaflet was last revised in .

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 European Medicines 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 European Medicines Agency web site: http://www.ema.europa.eu.

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 5-mL syringe [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 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 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

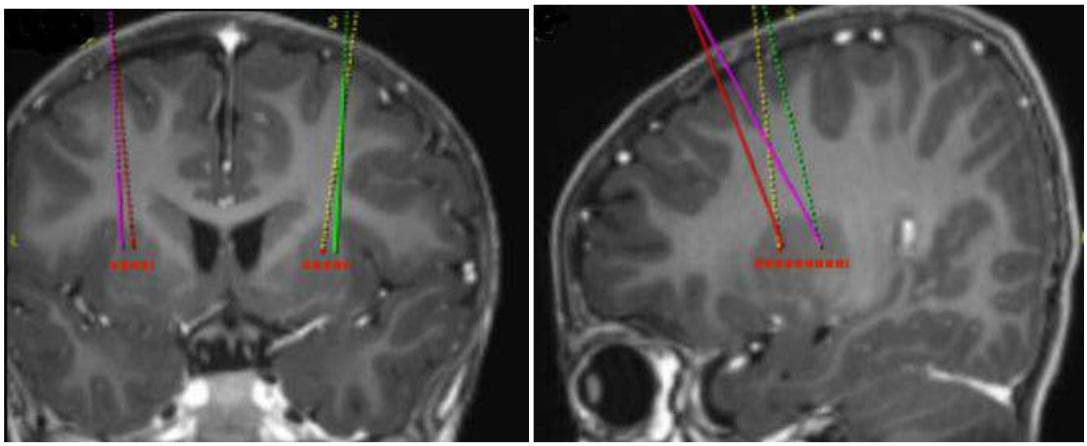
Intraputaminal use.

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 computerised tomography imaging examination 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 paediatric neurologist and with the neurosurgeon. 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.