# Summary of the risk management plan for Upstaza (eladocagene exuparvovec)

This is a summary of the risk management plan (RMP) for Upstaza. The RMP details important risks of Upstaza, how these risks can be minimised, and how more information will be obtained about Upstaza's risks and uncertainties (missing information).

Upstaza's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Upstaza should be used.

This summary of the RMP for Upstaza should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Upstaza's RMP.

## I. The medicine and what it is used for

Upstaza is authorised for the treatment of patients with AADC deficiency due to inherited recessive alleles from birth resulting in DDC gene mutations and with significant motor impairment (see SmPC for the full indication). It contains eladocagene exuparvovec as the active substance and it is given by intracerebral infusion into the putamen, a specific area of the brain.

Further information about the evaluation of Upstaza's benefits can be found in Upstaza's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/upstaza

## II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Upstaza, together with measures to minimise such risks and the proposed studies for learning more about Upstaza's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Upstaza, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Upstaza is not yet available, it is listed under 'missing information' below.

## II.A List of important risks and missing information

Important risks of Upstaza are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Upstaza. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | • Dyskinesia<br>• Procedural complications, including CSF leaks |
| Important potential risks | • Tumorigenicity<br>• Immunogenicity (Including cellular and humoral immunogenicity)<br>• Third party transmission |
| Missing information | • Long-term safety (>10 years)<br>• Use in children ≤18 months old |

## II.B Summary of important risks

| **Important identified risk: Dyskinesia** | |
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| Evidence for linking the risk to the medicine | Dyskinesia was the most frequently reported adverse event (88.5%) |
| Risk factors and risk groups | All patients with the AADC deficiency and chronic severe neurotransmitter deficiency. |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>• *SmPC sections 4.4 and 4.8; PIL section 2 and 4*<br>• *Information on time to recovery and use of dopamine antagonists to control symptoms*<br>• *Prescription only medicine*<br>**Additional risk minimisation measures:**<br>• *Provision of a surgical guide*<br>• *Controlled distribution through qualified treatment centres* |
| Additional pharmacovigilance activities | See section II.C of this summary for an overview of the post-authorisation development plan. |

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| **Important identified risk: Procedural complications, including CSF leaks** | |
| Evidence for linking the risk to the medicine | Clinical Trials and literature |
| Risk factors and risk groups | Patients undergoing intraputaminal infusion |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>• *SmPC sections 4.2, 4.4; PIL section 2*<br>• *Patient undergoes CT scan post-operatively for complications such as bleeding*<br>• *Information on monitoring patients for CSF leaks after administration*<br>• *Prescription only medicine*<br>**Additional risk minimisation measures:**<br>• *Provision of a surgical guide*<br>• *Controlled distribution through qualified treatment centres* |
| Additional pharmacovigilance activities | See section II.C of this summary for an overview of the post-authorisation development plan. |
| **Important potential risk: Tumorigenicity** | |
| Evidence for linking the risk to the medicine | This is an advanced therapeutic medicinal product (ATMP) specific risk consideration. |
| Risk factors and risk groups | Unknown |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>• *Prescription only medicine*<br>**Additional risk minimisation measures:**<br>• *None* |
| **Important potential risk: Immunogenicity** (Including cellular and humoral immunogenicity) | |
| Evidence for linking the risk to the medicine | Literature |
| Risk factors and risk groups | Unknown |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>• *SmPC sections 4.2, 4.4 and 4.8*<br>• *Information on constituents of the immune response including fever, skin rash, or shock. Information on when elevation of anti-AAV2 antibodies occurred in clinical trials and that these were not associated with an increase in severity, number of adverse events or decreased efficacy. Information on anti-capsid antibody levels in patients treated in the clinical trial programme are provided.*<br>• *Prescription only medicine*<br>**Additional risk minimisation measures:**<br>• *None* |
| Additional pharmacovigilance activities | See section II.C of this summary for an overview of the post-authorisation development plan. |
| **Important potential risk: Third party transmission** | |
| Evidence for linking the risk to the medicine | ATMP specific risk consideration - Environmental Risk Assessment |

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| Risk factors and risk groups | Healthcare workers involved in the preparation and administration of Eladocagene exuparvovec.<br><br>Healthcare workers or others involved in caring for the patient after administration, which may include those performing washing affected areas or changing dressings.<br><br>Close contacts of the treated individual (partners and family members) |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>*SmPC section 4.4 and 6.6*<br>Information on preparation of Upstaza and handling of the medication and what to do in the case of accidental exposure<br>**Additional risk minimisation measures:**<br>• *Pharmacy manual and patient alert card.* |
| Additional pharmacovigilance activities | See section II.C of this summary for an overview of the post-authorisation development plan. |
| **Missing information: Long-term safety (>10 years)** | |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>• *Prescription only medicine*<br>**Additional risk minimisation measures:**<br>• *None* |
| Additional pharmacovigilance activities | See section II.C of this summary for an overview of the post-authorisation development plan. |
| **Missing information: Use in children ≤18 months** | |
| Risk minimisation measures | **Routine risk minimisation measures**:<br>• *SmPC sections 4.2*<br>• *Prescription only medicine*<br>**Additional risk minimisation measures:**<br>• *None* |
| Additional pharmacovigilance activities | See section II.C of this summary for an overview of the post-authorisation development plan. |

## II.C Post-authorisation development plan

### *II.C.1* Studies which are conditions of the marketing authorisation or Specific Obligation under exceptional circumstances of Upstaza

The below two studies (PTC-AADC-MA-406 and AADC-1602 Long-term follow-up study) are imposed as Specific Obligation(SO) in the context of Marketing Authorisation under exceptional circumstances for efficacy reasons. Both the studies addresses the safety concerns of Dyskinesia, Procedural complications, including, CSF leaks, Tumorigenicity, Immunogenicity (including cellular and humoral immunogenicity), Third Party Transmission, Long-term safety (>10years), Use in children ≤ 18 months.

**Study short name:**

PTC-AADC-MA-406: A Two-Part Registry of Participants Diagnosed with Aromatic L Amino Acid Decarboxylase Deficiency (AADC-d) With or Without Treatment with Upstaza (Eladocagene Exuparvovec) (AADCAchieve).

**Purpose of the study:**

Part A of the registry will describe the natural history of AADC-d in participants on standard of care.

Part B of the registry will evaluate the long-term effectiveness and safety for participants treated with Upstaza (eladocagene exuparvovec) for a minimum of 10 years following gene therapy. The registry will also assess Motor development milestones, symptomology and also the quality of life of AADC deficiency patients.

**Study short name:** AADC-1602 Long-term follow-up study for existing patient population enrolled in the clinical studies AADC-CU/1601, AADC-010 and AADC-011.

**Purpose of the study:** To assess long-term durability of treatment and safety with eladocagene exuparvovec.

### *II.C.2 Other studies in post-authorisation development plan*

None.

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