OPINION ON MEDICINAL PRODUCTS

eladocagene exuparvovec

UPSTAZA 2.8 x 10 exp11 vector genomes/0.5 mL,

solution for infusion

First assessment

Adopted by the Transparency Committee on 7 December 2022

SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement for the treatment of patients aged 18 months and over with a clinical, molecular and genetically confirmed diagnosis of aromatic L-amino acid decarboxylase (AADC) deficiency associated with a severe phenotype.

Therapeutic improvement?

Therapeutic improvement in the current therapeutic pathway.

Role in therapeutic strategy?

There is no aetiological treatment of the disease to date. Treatment of a patient with AADC deficiency is essentially symptomatic, with a multidisciplinary neurological, orthopaedic, educational, psychological and social approach.

The medical need is currently unmet for the treatment of patients aged 18 months and over with a clinical, molecular and genetically confirmed diagnosis of aromatic L-amino acid decarboxylase (AADC) deficiency associated with a severe phenotype.

Role of the medicinal product

UPSTAZA (eladocagene exuparvovec) is a first-line treatment of patients aged 18 months and over with a clinical, molecular and genetically confirmed diagnosis of aromatic L amino acid decarboxylase (AADC) deficiency associated with a severe phenotype.

In clinical studies, the patients treated with UPSTAZA (eladocagene exuparvovec) had typical clinical characteristics of AADC deficiency such as oculogyric crises, hypotonia and development delay.

The marketing authorisation indication does not define an upper age limit, but experience is limited in patients over 12 years of age. The gain in motor function is more uncertain in older patients (brain plasticity, neural network integrity). It should also be possible to discuss gene therapy for these patients on a case-by-case basis by defining the objectives for each patient.

Complications associated with the surgical procedure (potentially including CSF leakage and pseudomeningocele) or exacerbations of symptoms of the underlying disease (apnoea, arterial hypotension, heart rhythm problems, bradycardia and cardiac arrest) following the surgical procedure and anaesthesia on account of adrenaline and noradrenaline deficiency and sympathetic nervous system dysfunction must be the subject of close postoperative monitoring. Hospitalisation for several days with follow-up on D7 and D14 appears to be appropriate.

Committee's conclusions

Clinical Benefit

- Aromatic L-amino acid decarboxylase (AADC) deficiency associated with a severe phenotype is characterised by limited or no motor development and total dependency, with a risk of premature death during the first ten years of life. AADC deficiency is a serious life-threatening disease with a significant impact on patient's and caregivers' quality of life.
- The proprietary medicinal product UPSTAZA (eladocagene exuparvovec) is a curative medicinal product.
- The efficacy/adverse effect ratio of UPSTAZA (eladocagene exuparvovec) is significant.
- No therapeutic alternative is available.
- UPSTAZA (eladocagene exuparvovec) is a first-line treatment of patients aged 18 months and over with a clinical, molecular and genetically confirmed diagnosis of aromatic L amino acid decarboxylase (AADC) deficiency associated with a severe phenotype.

Public health benefit

Considering:

- the severity of the disease and its rare nature,
- the unmet medical need,
- the partial response of UPSTAZA (eladocagene exuparvovec) to the identified need with an expected additional impact on morbidity, considering the findings observed in terms of efficacy and safety in the 3 non-comparative studies, with no evidence of an impact on mortality considering the short follow-up period of use of this medicinal product and on quality of life in the absence of furnished data,
- an expected, but non-demonstrated, additional impact in the absence of furnished data, on delivery of care and on the care and life pathway considering the specific mode of administration of this medicinal product and the follow-up required after its administration considering its characteristics, namely gene therapy,

UPSTAZA (eladocagene exuparvovec) is not likely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the clinical benefit of UPSTAZA (eladocagene exuparvovec) is significant in the marketing authorisation indication.

The Committee approves inclusion in the list of proprietary medicinal products approved for community use for the marketing authorisation indication and dosages.

Clinical Added Value

Considering:

- the clinical data available essentially based on 3 monocentric non-comparative clinical studies, including one retrospective study, including a total of 30 paediatric patients with AADC deficiency associated with a severe phenotype, followed for up to 60 months; the data in respect of use following the administration of UPSTAZA (eladocagene exuparvovec) to 3 patients in France being very fragmented,
- the findings of the 3 non-comparative clinical studies showing an improvement with respect to inclusion on motor development outcome measures such as “capable of holding head up completely” and “capable of sitting unassisted”, and to a lesser degree on the outcome measures “capable of standing with assistance” and “capable of walking with assistance”, and on other motor development parameters (gross and fine motor skills), cognitive and language development, motor symptoms (dystonia, oculogyric crises), weight gain and respiratory infections,
- the lack of adverse event reported linked with the specific mode of administration of UPSTAZA (eladocagene exuparvovec) and its overall favourable safety profile, but with limited follow-up, however, linked with administration in a single centre in the clinical studies, a limited sample of treated patients and maximum post-administration follow-up period of 60 months,
- the unmet medical need in this disease,

but:

- the lack of control group, while the mode of administration of UPSTAZA (eladocagene exuparvovec) did not allow a study versus placebo, a robust comparison to a well-described historic cohort would have enabled better quantification of the treatment effect with regard to the natural course of the disease,
- the lack of quality-of-life data in this disease with a significant impact on patients’ and caregivers’ quality of life,

the Committee deems that UPSTAZA (eladocagene exuparvovec) provides moderate clinical added value (CAV III) in the current therapeutic strategy which includes symptomatic treatments and supportive care.