EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/OD/0000024196
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Upstaza (eladocagene exuparvovec)
Treatment of aromatic L-amino acid decarboxylase deficiency
EU/3/16/1786

Sponsor: PTC Therapeutics International Limited

Note:

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substances(s) at the time of orphan designation	Recombinant adeno-associated viral vector serotype 2 carrying the gene for the human aromatic L-amino acid decarboxylase protein
Other name(s)	AADC deficiency gene therapy programme - PTC Therapeutics; AAV-hAADC-gene-therapy-PTC Therapeutics/National-Taiwan-University; AAV2-hAADC - PTC Therapeutics/National Taiwan University; AGIL-AADC; GT-AADC; PTC-AADC Gene therapies
International Non-Proprietary Name	Eladocagene exuparvovec
Tradename	Upstaza
Orphan condition	Treatment of aromatic L-amino acid decarboxylase deficiency
Sponsor's details:	PTC Therapeutics International Limited 5th Floor Grand Canal Plaza 3 Grand Canal Street Upper Dublin 4 D04 EE70 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Voisin Consulting S.A.R.L.
COMP opinion date	6 October 2016
EC decision date	18 November 2016
EC registration number	EU/3/16/1786
Post-designation procedural history	
Transfer of sponsorship	Transfer from Voisin Consulting S.A.R.L to Diamond BioPharm Limited - EC decision of 19 October 2017 2nd transfer from Diamond BioPharm Limited to Voisin Consulting S.A.R.L - EC decision of 27 September 2018 3rd transfer from Voisin Consulting S.A.R.L. to PTC Therapeutics International Limited - EC decision of 6 December 2018
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	M. O'Donovan / L. Barkholt
Applicant	PTC Therapeutics International Limited
Application submission date	11 January 2020
Procedure start date	28 January 2020
Procedure number	EMA/H/C/005352/0000
Invented name	Upstaza

Proposed therapeutic indication	Upstaza is indicated for the treatment of aromatic L-amino aciddecarboxylase (AADC) deficiency. Further information on Upstaza can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Upstaza
CHMP opinion date	19 May 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	D. Duarte / A. Magrelli
Sponsor's report submission date	31 January 2020
COMP discussion	10-12 May 2022
COMP opinion date (via written procedure)	23 May 2022

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2016 designation was based on the following grounds:

"The sponsor Voisin Consulting S.A.R.L. submitted on 20 July 2016 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing recombinant adeno-associated viral vector serotype 2 carrying the gene for the human AADC protein for treatment of aromatic L-amino acid decarboxylase (AADC) deficiency (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

For the purpose of orphan designation, the Committee for Orphan Medicinal Products (COMP) considered that the active substance should be renamed as "recombinant adeno-associated viral vector serotype 2 carrying the gene for the human aromatic L-amino acid decarboxylase protein".

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing recombinant adeno-associated viral vector serotype 2 carrying the gene for the human aromatic L-amino acid decarboxylase protein was considered justified based on preliminary clinical data in patients with the condition which showed improvements in motor and cognitive function;
- the condition is life-threatening due to death caused by multiple organ failure, sepsis, heart failure and pneumonia and chronically debilitating due to profound autonomic and haemodynamic regulatory dysfunction and potential implications regarding regulation of cerebrovascular blood flow. Gastroesophageal reflux is observed in the majority of patients and significantly contributes to feeding and swallowing difficulties;
- the condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing recombinant adeno-associated viral vector serotype 2 carrying the gene for the human aromatic L-amino acid decarboxylase protein as an orphan medicinal product for the orphan indication: treatment of aromatic L-amino acid decarboxylase deficiency".

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Aromatic L-amino acid decarboxylase (AADC) deficiency is an important neuro-metabolic disease in children. Children with AADC deficiency usually present with severe developmental delay, oculogyric crises (an eyeball movement disorder), generalized hypotonia, paroxysmal dystonia, and autonomic dysfunction (Shih et al, PLOS August 2013 Volume 8 Issue 8).

AADC deficiency is an autosomal recessive neurotransmitter disorder. It is caused by a deficiency in AADC due to a mutation in the AADC gene (DDC) on chromosome 12p12.3-p12.The pathogenetic mechanism of AADC deficiency and its role in brain development remain unclear. AADC is responsible for the decarboxylation step in the catecholamine and dopamine biosynthesis. Dopamine and serotonin can be synthesized by AADC from L-3,4- dihydroxyphenylalanine and 5-hydroxytryptophan, respectively.

A deficiency in AADC will lead to reduced biogenic monoamines, including dopamine, norepinephrine, epinephrine, and serotonin. AADC deficiency has been reported in almost 80 patients worldwide. The most consistent features associated with this deficiency are those of combined dopamine and noradrenaline deficiency. The signs of dopamine deficiency include hypokinesia, rigidity, dystonia (with or without diurnal variations), distal chorea, and oculogyric crises. The clinical features of noradrenaline insufficiency include ptosis, miosis, profuse oropharyngeal secretions, postural hypotension, autonomic dysfunction, and temperature instability. Similarly, symptoms of serotonin deficiency include sleep disorders, memory and learning disabilities, and behavioural disturbances. Hypotonia and oculogyric crises are the most common clinical signs noted across all reported patients.

The characteristic pattern of abnormalities in cerebrospinal fluid in patients with AADC deficiency includes low homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5- HIAA) levels, and elevated L-3,4-dihydroxyphenylalanine (LDOPA) and 3-o-methyldopa levels.

The approved therapeutic indication "*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"* falls within the scope of the designated orphan condition "treatment of aromatic L-amino acid decarboxylase deficiency".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

Patients with AADC suffer from severe movement disorders, abnormal eye movements, autonomic symptoms and neurological impairment. Causes of death have included multiple organ failure), sepsis (2), heart failure (1) and pneumonia (1) (Hwu, Muramatsu et al., 2012).

AADC patients present a profound autonomic and hemodynamic regulatory dysfunction and potential implications regarding regulation of cerebrovascular blood flow. Such issues may be particularly important during anaesthesia, when reflex responses are blunted (Swoboda, Saul et al., 2003). Gastrointestinal issues are also important symptoms to consider in AADC-deficient patients. Gastroesophageal reflux is observed in the majority of patients and significantly contributes to feeding and swallowing difficulties and poor quality-of-life.

Number of people affected or at risk

The sponsor has submitted a prevalence estimate based on several recent publications. These are summarised below:

Table. 1

Himmelreich 2019	Aromatic amino acid decarboxylase deficiency: Molecular and metabolic basis and therapeutic outlook	Molecular Genetics and Metabolism, https://doi.org/10.1016/j.ymgme.2019.03.009
Whitehead 2018	Estimated prevalence of aromatic l-amino acid decarboxylase (AADC) deficiency in the United States, European Union, and Japan	30 November 2018, Biology
Wassenberg 2017	Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency	Orphanet Journal of Rare Diseases (2017) 12:12
Hyland 2020	Prevalence of Aromatic l-Amino Acid Decarboxylase Deficiency in At-Risk Populations	Pediatric Neurology Volume 106, May 2020, Pages 38-42

Whitehead and colleagues (2018) used whole genome sequencing and whole-exome sequencing to probe genomic deoxyribose nucleic acid (DNA) sequence databases for the frequency of pathogenic DDC variant alleles in the United States (US), EU, and Japan. In this study databases were probed for known pathogenic variants (those already observed in patients with AADC deficiency) and variants predicted to be pathogenic based on the impact of missense and splice variants. Based on analysis of approximately 200 000 individual genomes, 33 previously known and 183 predicted pathogenic variants were identified. Based on formulae for deriving the frequency of individuals affected at birth from pathogenic allele frequencies, the predicted birth rates of individuals with AADC deficiency were estimated to be 1/118 000 in the EU, which translated into 45 births/year. These assumptions lead to a current estimate of about 853 AADC-deficiency patients in the EU.

In their publication, Wassenberg et al, 2017 note that only 123 unique patients with AADC-deficiency have been described and catalogued worldwide however that there could be approximately 1 800

(853+840+125=1 818) patients in the EU, US and Japan combined alone when potentially undiagnosed individuals are added (Whitehead 2018).

Hyland et al 2018 took a different methodological approach by screening biological samples from 19 684 US patients with neurologic deficits of unknown origin obtained between 2008 and 2016 (Hyland 2018, Himmelreich 2019). The majority (n=19 577) were screened for abnormal CSF profiles (elevated L-DOPA breakdown product, reduced levels of HVA and 5HIAA); the remainder were screened for reduced plasma AADC activity (n=65) or, via DNA sequencing, for known pathogenic DDC variants (n=42). A total of 36 new patients with AADC deficiency were identified (22 via abnormal CSF profile, 9 via reduced plasma AADC, 5 via sequencing) from the 19,684 screened samples (0.183%); the mean age of newly identified AADC-deficiency patients was 4.3 years, and there was an equal gender mix (18 males/18 females). Based on previous studies, the authors concluded that the newborn prevalence of AADC deficiency is approximately 1/42 000 (Hyland 2018).

The new analysis has increased the estimated number of AADC-deficiency patients in the EU from 62 (number form initial ODD application) to 853 (Himmelreich 2019). In this estimate most AADC-deficiency patients in the EU are not accurately diagnosed. Given that only 123 unique patients with AADC deficiency have been described and catalogued worldwide, it is clear that most individuals with this genetic disorder remain undiagnosed.

For the revised prevalence, the sponsor proposes an estimate of 1 in 118,000 prevalence or 0.1 in 10,000 in the European Union. The COMP could accept this revised prevalence estimate for the purpose of the maintenance of the orphan designation.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are currently no authorised treatments in Europe for the condition. Treatment of AADC deficiency is supportive. The most common first-line treatments are bromocriptine and pyridoxine with dosages ranging between 40 mg/day and 1,800 mg/day (4.0–81 mg/kg/day) and 1.0–45.5 mg/day (0.013–4.0 mg/kg/day), respectively. Bromocriptine is a dopamine receptor agonist with high affinity for D2-like receptors and has been prescribed to correct motor deficit like hypokinesia, axial hypotonia, limb hypertonia, dystonia and choreoathetosis. However, its effect has varied among individuals. Pyridoxine or vitamin B6 is also given to patients to boost residual AADC activity with a cofactor excess. Recent guidelines have been published; Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency Wassenberg et al. Orphanet Journal of Rare Diseases (2017) 12:12. They propose the treatment algorithm reproduced below.

Figure 1.

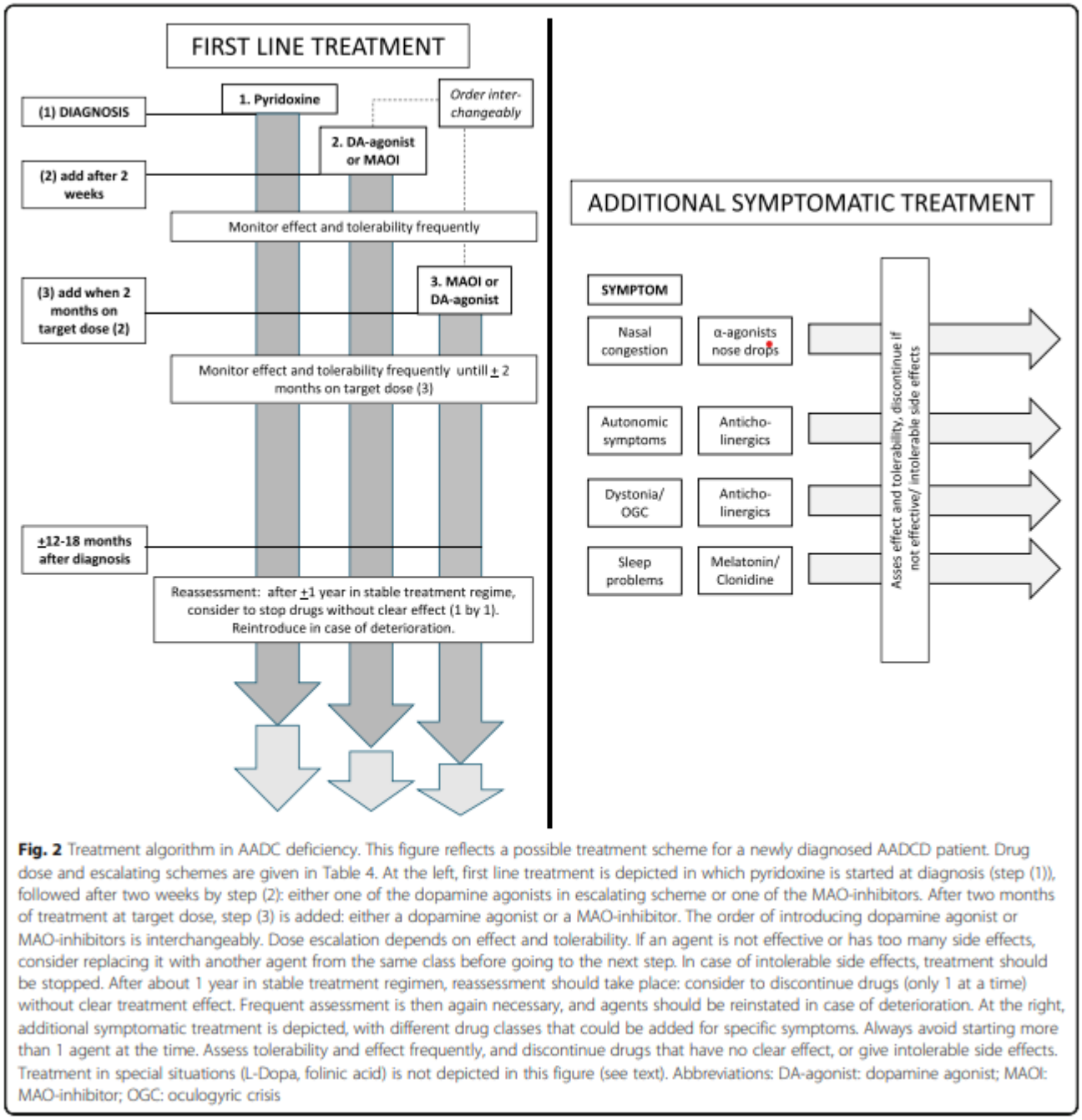

Fig. 2 Treatment algorithm in AADC deficiency. This figure reflects a possible treatment scheme for a newly diagnosed AADCD patient. Drug dose and escalating schemes are given in Table 4. At the left, first line treatment is depicted in which pyridoxine is started at diagnosis (step (1)), followed after two weeks by step (2): either one of the dopamine agonists in escalating scheme or one of the MAO-inhibitors. After two months of treatment at target dose, step (3) is added: either a dopamine agonist or a MAO-inhibitor. The order of introducing dopamine agonist or MAO-inhibitors is interchangeably. Dose escalation depends on effect and tolerability. If an agent is not effective or has too many side effects, consider replacing it with another agent from the same class before going to the next step. In case of intolerable side effects, treatment should be stopped. After about 1 year in stable treatment regimen, reassessment should take place: consider to discontinue drugs (only 1 at a time) without clear treatment effect. Frequent assessment is then again necessary, and agents should be reinstated in case of deterioration. At the right, additional symptomatic treatment is depicted, with different drug classes that could be added for specific symptoms. Always avoid starting more than 1 agent at the time. Assess tolerability and effect frequently, and discontinue drugs that have no clear effect, or give intolerable side effects. Treatment in special situations (L-Dopa, folinic acid) is not depicted in this figure (see text). Abbreviations: DA-agonist: dopamine agonist; MAOI: MAO-inhibitor; OGC: oculogyric crisis

Significant benefit

Not applicable.

4. COMP position adopted on 23 May 2022

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of aromatic L-amino acid decarboxylase deficiency (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening due to death caused by multiple organ failure, sepsis, heart failure and pneumonia and chronically debilitating due to profound autonomic and haemodynamic regulatory dysfunction and potential implications regarding regulation of cerebrovascular blood flow. Gastroesophageal reflux is observed in the majority of patients and significantly contributes to feeding and swallowing difficulties. The disease also affects the nervous system, with hypotonia, hypokinesia, oculogyric crises, sweating, signs of autonomic dysfunction and a severe delay in psychomotor development;
- there is, at present, no satisfactory method for the treatment of aromatic L-amino acid decarboxylase deficiency that has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Upstaza, recombinant adeno-associated viral vector serotype 2 carrying the gene for the human aromatic L-amino acid decarboxylase protein, eladocagene exuparvovec for treatment of aromatic L-amino acid decarboxylase deficiency (EU/3/16/1786) is not removed from the Community Register of Orphan Medicinal Products.