Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Eladocagene exuparvovec (Aromatic-L-amino acid decarboxylase (AADC) deficiency, ≥ 18 months)

of 2 February 2023

At its session on 2 February 2023, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. **Annex XII shall be amended in alphabetical order to include the active ingredient Eladocagene exuparvovec as follows:**

Courtesy translation – only the German version is legally binding.

Eladocagene exuparvovec

Resolution of: 2 February 2023
Entry into force on: 2 February 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 18 July 2022):

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.

Therapeutic indication of the resolution (resolution of 2 February 2023):

See therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Eladocagene exuparvovec is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5, Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5, Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

<u>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</u>

Extent of the additional benefit and significance of the evidence of eladocagene exuparvovec:

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

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Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	↑	Advantage in the motor milestones "Full head control" and "Sitting unassisted".
Health-related quality of life	∅	No data available.
Side effects	n.a.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

AADC-010 study: prospective, single-centre, single-arm phase I/II study; children > 2 years with confirmed diagnosis of AADC deficiency

AADC-011 study: prospective, single-centre, single-arm phase IIb study; children aged 2 to 6 years with confirmed diagnosis of AADC deficiency

AADC-CU/1601 study: single-centre, single-arm study (compassionate use program) followed by retrospective follow-up study; children aged 2 to 6 years with confirmed diagnosis of AADC deficiency

AADC-1602 study: Long-term follow-up of patients from the studies AADC-010, AADC-011, AADC-CU/1601; data cut-off 15 July 2022

External Control Study: "*natural history data base*" (NHDB); natural history cohort from published cases (research from July 2022)

Indirect comparison: Eladocagene exuparvovec (AADC-1602) vs natural history (NHDB)

[1] Data from the dossier assessment of the G-BA (published on 15. November 2022), and from the amendment to the dossier assessment from 18 January 2023, unless otherwise indicated.

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Mortality

AADC-1602 study Endpoint	**Eladocagene exuparvovec**	
	N	Patients with event n (%)
Overall mortality	21	6 (28.6)

Morbidity

Endpoint	**Eladocagene exuparvovec (AADC-1602)**		**NHDB**		**Eladocagene exuparvovec vs NHDB**
	N	n (%)	N	n (%)	Hazard ratio [95%-CI][a]; P value[a]
Achievement of milestones based on PDMS-2					
Full head control[b]	21	14 (66.7)	46	3 (6.5)	8.6 [2.5; 30.1]; 0.0007
Sit unassisted[c]	21	13 (61.9)	46	2 (4.3)	10.1 [2.3; 45.2]; 0.0024

Endpoint	**Eladocagene exuparvovec (AADC-1602)**		**NHDB with known genetic defect**		**Eladocagene exuparvovec vs NHDB with known genetic defect**
	N	n (%)	N	n (%)	Hazard ratio [95%-CI][a]; P value[a]
Achievement of milestones based on PDMS-2					
Full head control[b]	21	14 (66.7)	35	2 (5.7)	11.0 [2.5; 48.5]; 0.0015
Sit unassisted[c]	21	13 (61.9)	35	2 (5.7)	8.7 [2.0; 38.6]; 0.0045

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AADC-1602 study Endpoint	**Eladocagene exuparvovec**	
	N	n (%)
Achievement of milestones based on PDMS-2		
Walk with assistance[d,e]	21	4 (19.0)
	N	n (%) LS mean difference [95% CI][f]
PDMS-2 total value[g]		
Month 60 change from baseline	21	15 (71) 115.0 [93.0; 136.9]
AIMS total value[h]		
Month 60 change from baseline	21	13 (62) -[i]
	N[j]	n (%) LS mean difference [95% CI][f]
BSID-III[g]		
Cognitive scale Month 60 change from baseline	13	10 (77) 21.7 [17.3; 26.1]
Expressive communication Month 60 change from baseline	13	10 (77) 6.4 [3.7; 9.1]
Receptive communication Month 60 change from baseline	13	10 (77) 7.6 [6.2; 8.9]

Health-related quality of life

Health-related quality of life was not collected.

Side effects

Endpoint	**AADC-010 study[k]**		**AADC-011 study[k]**		**AADC-CU/1601 study[k]**	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
Adverse events (presented additionally)	10	10 (100)	3	3 (100)	8	8 (100)
Serious adverse events (SAE)	10	8 (80)	3	3 (100)	8	8 (100)
SAEs with incidence ≥ 20 % in one of the studies according to MedDRA system organ class Preferred term						
Infections and infestations	10	8 (80.0)	3	3 (100)	8	6 (75.0)

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Endpoint	AADC-010 study[k]		AADC-011 study[k]		AADC-CU/1601 study[k]	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)
Gastroenteritis	10	4 (40.0)	3	2 (66.7)	8	4 (50.0)
Pneumonia	10	6 (60.0)	3	2 (66.7)	8	6 (75.0)
Pneumonia after procedure	10	2 (20.0)	3	0 (0)	8	0 (0)
Upper respiratory tract infection	10	2 (20.0)	3	1 (33.3)	8	1 (12.5)
Pneumonia due to Haemophilus	10	0 (0)	3	1 (33.3)	8	0 (0)
Viral pneumonia	10	0 (0)	3	1 (33.3)	8	0 (0)
Respiratory, thoracic and mediastinal disorders	10	3 (30.0)	3	0 (0)	8	5 (62.5)
General disorders and administration site conditions	10	3 (30.0)	3	0 (0)	8	2 (25.0)[2)]
Fever	10	3 (30.0)	3	0 (0)	8	1 (12.5)
Vascular disorders	10	2 (20.0)	3	0 (0)	8	4 (50.0)
Hypovolemic shock	10	1 (10.0)	3	0 (0)	8	2 (25.0)
Congenital, familial and genetic disorders	10	2 (20.0)	3	0 (0)	8	0 (0)
Developmental dysplasia of the hip	10	2 (20.0)	3	0 (0)	8	0 (0)
Gastrointestinal disorders	10	1 (10)	3	1 (33.3)	8	5 (62.5)
Upper gastrointestinal bleeding	10	0 (0)	3	0 (0)	8	2 (25.0)
Metabolism and nutrition disorders	10	1 (10.0)	3	3 (100)	8	1 (12.5)
Dehydration	10	1 (10.0)	3	3 (100)	8	1 (12.5)
Nervous system disorders	10	1 (10.0)	3	0 (0)	8	2 (25.0)
Cardiac disorders	10	1 (10.0)	3	0 (0)	8	0 (0)
Cyanosis	10	0 (0)	3	0 (0)	8	2 (25.0)
Musculoskeletal and connective tissue disorders	10	0 (0)	3	1 (33.3)	8	2 (25.0)

[a] Post hoc calculated using Cox model. No information on the model structure identified.
[b] Fulfilment of PDMS-2 item 10 of the "gross motor skills - balance" subscale by the child sitting supported at the hip and aligning the head while turning the head to follow a toy for 8 seconds.
[c] Completing PDMS-2 item 14 of the "gross motor skills - balance" subscale by the child sitting unassisted and maintaining balance in a seated position for 60 seconds.

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Endpoint	AADC-010 study[k]		AADC-011 study[k]		AADC-CU/1601 study[k]	
	N	Patients with event n (%)	N	Patients with event n (%)	N	Patients with event n (%)

[d] Data from the written statement of the pharmaceutical company.
[e] Achieving a score of "2" on PDMS-2 item 34 of the "gross motor skills - movement" subscale by having the child walk at least 8 feet (2.4 metres) with alternating steps, with the examiner standing beside the child and holding only one of the child's hands.
[f] Repeated measures analysis with time, age at gene therapy (in months) and baseline as fixed effects, taking into account repeated measures per subject.
[g] Higher values stand for better function. No information was identified as to the maximum total value that can be achieved.
[h] The total value can take on values between 0 and 58, with higher values representing better motor development.
[i] Percentage of existing values too low compared to ITT population.
[j] Includes studies AADC-010 and AADC-011.
[k] Data cut-off of 15 July 2022.

Abbreviations:
AIMS: Alberta Infant Motor Scale; BSID-III: Bayley Scales of Infant Development - Third Edition; CI: confidence interval; LS: Least Squares; PDMS-2: Peabody Developmental Motor Scales - Second Edition; SAE: serious adverse events.

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 4 - 30 patients

3. Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Upstaza (active ingredient: eladocagene exuparvovec) at the following publicly accessible link (last access: 14 December 2022):

https://www.ema.europa.eu/en/documents/product-information/upstaza-epar-product-information_en.pdf

By resolution of 20 October 2022, the necessity of a resolution pursuant to Section 136a, paragraph 5 SGB V in accordance with Chapter 9 Section 5 Sentence 2 VerfO was established for the use of eladocagene exuparvovec in the therapeutic indication "Treatment of aromatic-L-amino acid decarboxylase (AADC) deficiency". As soon as corresponding regulations on quality assurance measures according to the ATMP Quality Assurance Guideline come into force, they must also be observed.

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Initiation and monitoring of treatment with eladocagene exuparvovec must be carried out in a treatment facility specialising in stereotactic neurosurgery by a qualified neurosurgeon under controlled aseptic conditions.

In accordance with the requirements of the European Medicines Agency (EMA) regarding additional risk minimisation measures, the pharmaceutical company shall provide training material (i.e. the surgical guide and the pharmacy manual) for healthcare professionals (i.e. neurologists, neurosurgeons and pharmacists) and a patient identification card.

The training material contains, in particular, instructions on how to prepare and perform the stereotactic administration of eladocagene exuparvovec. The surgical guide for eladocagene exuparvovec is designed to ensure correct use of the product to minimise risks associated with administration, including leakage of cerebrospinal fluid. The risk management plan details that the training material for healthcare professionals will include relevant information for the safe handling and disposal of the materials concerned 14 days after the administration of the product, together with information regarding the exclusion from donation of blood, organs, tissues, cells for transplantation after the administration of eladocagene exuparvovec. The pharmacy manual contains information on receipt, storage, dispensing, preparation, return and/or destruction and traceability of the product. Prior to scheduling the procedure, a representative of the pharmaceutical company will go over the surgical guide for eladocagene exuparvovec with the neurosurgeon and the pharmacy manual with the pharmacist.

The criteria for treatment facilities should include the following:

- The presence of or collaboration with a neurosurgeon with experience in stereotactic neurosurgery who is able to administer eladocagene exuparvovec;
- Existence of a hospital pharmacy that can handle and prepare adeno-associated virus vector-mediated gene therapy products;
- Ultra-low temperature freezers (≤ -65 °C) available within the treatment facility pharmacy for treatment storage.

This medicinal product was approved under "special conditions". This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product.

The European Medicines Agency will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Eladocagene exuparvovec[2]	€ 4,165,000.00

[2] Eladocagene Exuparvovec is used once.

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Designation of the therapy	Annual treatment costs/ patient
Intraputaminal infusion	approx. € 13,253.99[3]

Cost of the clinic pack plus value added tax of 19% (LAUER-TAXE® last revised: 15 January 2023)

Costs for additionally required SHI services: not applicable

5. Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with eladocagene exuparvovec

Medicinal products with the following new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with eladocagene exuparvovec for the treatment of AADC deficiency with a severe phenotype on the basis of the marketing authorisation granted under Medicinal Products Act:

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

No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

II. Entry into force

1. The resolution will enter into force on the day of its publication on the internet on the website of the Federal Joint Committee on 2 February 2023.

2. The period of validity of the resolution is limited to 15 February 2028.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 2 February 2023

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken

[3] Shown are the costs for an inpatient procedure.

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