Gemeinsamer Bundesausschuss

# Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

**Contents**

## 1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products approved for novel therapies within the meaning of Section 4, paragraph 9 Medicinal Products Act, there is an obligation to submit evidence in accordance with Section 35a, paragraph 1, sentence 3 SGB V. Medical treatment with such a medicinal product is not subject to the assessment of examination and treatment methods according to Sections 135, 137c or 137h.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit

assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published online and is part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was 15 August 2022 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA for the first placing on the (German) market of the active ingredient eladocagene exuparvovec. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 15 August 2022.

Eladocagene exuparvovec "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" 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. Eladocagene exuparvovec concerns a gene therapy within the meaning of Section 4, paragraph 9 Medicinal Products Act.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 November 2022 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G12-01) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of eladocagene exuparvovec.

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

## 2.1 Additional benefit of the medicinal product

### 2.1.1 Approved therapeutic indication of Eladocagene exuparvovec (Upstaza) in accordance with the product information

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 the approved therapeutic indication

### 2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of eladocagene exuparvovec is assessed as follows:

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

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

**Justification:**

For the benefit assessment of eladocagene exuparvovec, the pharmaceutical company submits the single-arm studies AADC-010, AADC-011, AADC-CU/1601 and the long-term follow-up study AADC-1602. In addition, the pharmaceutical company submits a natural history cohort (NHDB) from published cases.

AADC-010 study: The AADC-010 study is an open-label, single-arm, single-centre, prospective phase I/II study to evaluate the safety and efficacy of eladocagene exuparvovec in children > 2 years of age with a confirmed diagnosis of AADC deficiency. 10 patients were enrolled in the study. Patients received a single injection of eladocagene exuparvovec into the brain and were initially followed up for up to 5 years. The study ended on 31 December 2021.

AADC-011 study: This is an open-label, single-arm, single-centre, prospective phase IIb study to assess the safety and efficacy of eladocagene exuparvovec in children aged 2 to 6 years with a confirmed diagnosis of AADC deficiency. The active ingredient was used in two doses ($1.8 \times 10^{11}$ Vg; $2.4 \times 10^{11}$ Vg), whereby only the patients treated with the approved dose of $1.8 \times 10^{11}$ Vg (n = 3) are relevant for the benefit assessment. After the administration of eladocagene exuparvovec into the brain, the children were followed up for up to 12 months. At month 13, a final telephone visit was made to monitor safety. The end of the study was scheduled for January 2022.

The primary endpoint of the AADC-010 and AADC-011 studies was the measurement of motor function using the Peabody Developmental Motor Scales - Second Edition (PDMS-2). This determined the proportion of subjects with full head control, who could sit unassisted, could stand with support and could walk with assistance. Secondary endpoints included Alberta Infant Motor Scale (AIMS) and Bayley Scales of Infant Development - Third Edition (BSID-III)

surveys, body weight changes, AADC-related symptoms, muscle power and deep tendon reflexes.

AADC-CU/1601 study: The AADC-CU study is a prospective, single-arm, single-centre study of eladocagene exuparvovec administration in a compassionate use program. Children between 2 and 6 years of age with a confirmed diagnosis of AADC deficiency received eladocagene exuparvovec. The AADC-1601 study is a retrospective, single-arm, single-centre study to follow up the efficacy and safety of treatment with eladocagene exuparvovec in patients with AADC deficiency from the AADC-CU study. The data collection has taken place on the basis of the medical records. 8 patients were included and followed up to month 60. Primary endpoints were changes in motor and mental development and changes in the neurotransmitter metabolites HVA or 5-HIAA in the cerebrospinal fluid. Secondary endpoints included changes in body weight.

AADC-1602 study: Patients with appropriate consent from the AADC-010, AADC-011 and AADC-CU/1601 studies were included and followed up in the long-term follow-up study AADC-1602. The pharmaceutical company has submitted a data cut-off dated 15 July 2022. According to the pharmaceutical company, this forms the basis for approval by the FDA (U.S. Food and Drug Administration).

*Indirect comparisons*

The pharmaceutical company submits indirect comparisons without a bridge comparator for the endpoints mortality and motor function as part of the benefit assessment. For this purpose, the pharmaceutical company compares the data of the long-term follow-up study AADC-1602 (data cut-off 15 July 2022) with a natural history cohort (NHDB).

To form the NHDB, the pharmaceutical company conducts a systematic search for published AADC cases.

The 2017 consensus guideline[2] identified and published a natural history cohort of 117 confirmed AADC cases, 103 of which had sufficient information for severity classification. 82 children were classified as "severe" who had "no or very limited developmental milestones (fully dependent)". This cohort forms the basis of the indirect comparison ("Wassenberg" cohort) used by the EMA for the marketing authorisation of eladocagene exuparvovec. The "Wassenberg" cohort was not used due to the limited source data and lack of timeliness.

The pharmaceutical company conducted a renewed search (until July 2022). This identified 185 AADC cases with sufficient patient data, 163 of which were not involved in the eladocagene exuparvovec development programme. Furthermore, the patients had to have reached the earliest study enrolment age defined for the clinical studies of at least 24 months alive and at the same time without full head control. 46 children were identified who met these requirements. This comparator cohort was also submitted as part of the approval process, but was not used by the EMA due to the small sample size.

In addition, the pharmaceutical company is submitting time-to-event analyses for the achievement of motor milestones in patients from the AADC-1602 study compared to NHDB with known genetic AADC defect (n = 35).

The indirect comparisons presented for mortality and morbidity have considerable methodological limitations.

[2] Wassenberg T, Molero-Luis M, Jeltsch K, Hoffmann GF, Assmann B, Blau N, et al. Consensus guideline for the diagnosis and treatment of aromatic l-amino acid decarboxylase (AADC) deficiency. Orphanet J Rare Dis 2017;12(1):12.

Due to the lack of proof of structural equality, the indirect comparison is assessed as uncertain. There is no information on known disease-modifying factors that could be considered as possible effect modifiers. Furthermore, patient characteristics are only available for a few characteristics. No information on symptom-oriented therapies is available for the NHDB population.

Furthermore, it should be noted that the children in the AADC studies were a median of 51 months old at baseline. This means that the median age was significantly above 24 months, whereby only the lack of head control at month 24 was decisive for the NHDB for inclusion. Children who died prematurely could therefore not be included in the AADC studies. However, if these children were recorded in scientific publications, they could be included in the NHDB. Consequently, there is an immortal time bias to the advantage of eladocagene exuparvovec, as early events could not occur in the intervention. In addition, it cannot be ruled out that due to the different age at baseline, patients with a particularly severe course of disease and premature death are predominantly recorded in the NHDB.

Furthermore, the observation times of the NHDB and AADC populations differ greatly. The median age at the last observation point for the AADC population was 117 months (min; max: 41.1; 206.8) versus a median age of 63 months (min; max: 24; 228) at the NHDB. No information is available on the rules or reasons for censoring, which occurred at a very high rate of 93.5% in the NHDB cohort in particular.

Furthermore, with regard to the time of diagnosis, the median age of the NHDB children was 28 months. Thus, the children in the NHDB were older than the children in the AADC-010 (10.5 months), AADC-011 (9 months) and AADC-1601 (15 months) studies at this time. It is unclear to what extent the later diagnosis in the NHDB influenced access to symptom-oriented therapies and whether these therapies were equally available regardless of the healthcare context.

Against the background of the insufficiently proven structural equality of the two study populations, the indirect comparison is not classified as sufficiently valid and cannot be used for the benefit assessment. However, the NHDB documents a deterministic natural course of the disease in children with AADC deficiency, in which the motor milestones are not reached by the vast majority of patients. Therefore, the dramatic effects of eladocagene exuparvovec in the milestone analyses compared to the natural history of the disease can be considered for the benefit assessment.

Mortality

There were 6 deaths in the long-term follow-up study AADC-1602 at the 15 July 2022 data cut-off.

Morbidity

*Peabody Developmental Motor Scales - Second Edition (PDMS-2)*

The Peabody Developmental Motor Scales - Second Edition (PDMS-2) was used to determine motor skills. The PDMS-2 is a standardised test that measures gross and fine motor skills in infants and children from birth to 5 years of age. Each of the 249 items corresponds to a specific motor skill assessed by an examiner on a 3-point scale from 0 to 2. Here, "2" represents the maximum score, i.e. the specified criteria are completely fulfilled. With a "1", the child's performance shows a clear similarity to the criteria for coping with the task, but the criteria are not fully met. Higher values stand for better function. In the AADC studies, the test score was changed for simplicity so that only "0" for "ability absent" and "2" for "ability

present" were recorded. The pharmaceutical company states in his written statement that intermediate values ("1") were evaluated as not achieved ("0"). The evaluation took place as raw values and not against the norm population. Based on this survey, the pharmaceutical company derives the motor milestones "full head control", "sitting unassisted", "standing without assistance" and "walking with assistance" in the studies AADC-010, AADC-011, AADC-CU/1601 and the subsequent long-term follow-up study AADC-1602.

The change in PDMS-2 total value between baseline and month 60 was 115 points for the long-term follow-up study AADC-1602. The changes indicate that the children had better function compared to baseline. No information was identified as to what maximum the PDMS-2 total value can assume. Therefore, a further interpretation of these changes is not possible.

For an indirect comparison of the endpoints "achievement of motor milestones", the data cut-off of 15 July 2022 of the long-term follow-up study AADC-1602 is presented with the natural history cohort. The results of the time-to-event analysis on the milestones "full head control" and "sitting unassisted" show very large effects to the advantage of eladocagene exuparvovec, which are in the range of "dramatic effects". An evaluation for the next defined milestone ("standing with assistance") was not provided. The group difference in the following milestone "walking with assistance" did not reach statistical significance.

*Bayley Scales of Infant Development - Third Edition (BSID-III), Language Scale and Cognitive Scale*

The Bayley Scales of Infant Development - Third Edition (BSID-III) is a standardised, norm-referenced assessment of developmental functioning in infants and young children up to 42 months. The instrument is divided into 5 domains: cognition, language, motor, socio-emotional and adaptive behaviour. In the studies AADC-010 and AADC-011 and the subsequent long-term follow-up study AADC-1602, only the subscales "cognitive behaviour" and "language behaviour" were used.

Compared to baseline, a change of 22 points was achieved for the pooled AADC population in the cognitive scale at month 60. Smaller changes were seen in the language scales; for the expressive communication scale there was a change of 6 points between baseline and month 60 and for the receptive communication scale there was a change of 8 points at month 60.

Since information on possible maximum values of the scales is missing, no further statements can be made besides the positive direction of the changes for an improvement of the function.

*Alberta Infant Motor Scale (AIMS)*

The Alberta Infant Motor Scale (AIMS) is an observational tool to identify delayed motor development from birth to independent walking. The observational tool was used in the AADC-010, AADC-011 and AADC-CU/1601 studies and the subsequent long-term follow-up study AADC-1602.

The change in the AIMS total value for study AADC-1602 between baseline and month 36 was 25 points.

With a maximum total value of 58 points and the very low baseline scores in the AADC studies, it can therefore be assumed that motor function is better at this point in the study participants compared to baseline.

Quality of life

Health-related quality of life was not collected.

Side effects

Adverse events were recorded in patients in the AADC-010, AADC-011 and AADC-CU/1601 studies as part of the long-term follow-up study AADC-1602.

Adverse events occurred in all patients up to the time of the data cut-off. Serious adverse events were observed in almost all study participants.

Overall assessment

For eladocagene exuparvovec 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, results of the single-arm long-term follow-up study AADC-1602 are available on the endpoints of mortality, morbidity and side effects. In addition, a non-adjusted indirect comparison without a bridge comparator was presented for the endpoints mortality and the morbidity endpoint "achievement of motor milestones". For this purpose, the pharmaceutical company compares the data of the long-term follow-up study AADC-1602 (data cut-off 15 July 2022) with a natural history cohort (NHDB).

The indirect comparison presented could not be used due to the described limitations.

Even if the indirect comparison cannot be used for the benefit assessment, the NHDB documents a deterministic natural course of the disease in children with AADC deficiency, in which the motor milestones are not reached by the vast majority of patients. Therefore, the dramatic effects shown in the long-term follow-up study AADC-1602 can be considered in the milestone analyses for the benefit assessment and advantages of eladocagene exuparvovec can be derived with reasonable certainty for the endpoints "achieving full head control" and "sitting unassisted" compared to natural disease progression.

In the absence of robust data for a comparative assessment, it is not possible to quantify the magnitude of the additional benefit based on the data presented.

In addition, due to missing data on quality of life and missing comparative data on mortality and the safety profile of eladocagene exuparvovec, there are relevant uncertainties that do not allow an assessment of the magnitude of the additional benefit.

Overall, a non-quantifiable additional benefit is derived for eladocagene exuparvovec because the scientific data basis does not allow quantification.

Significance of the evidence

Only single-arm data could be considered for the benefit assessment.

The risk of bias of the single-arm study data is estimated to be high at study and endpoint level.

The significance of the evidence is classified as 'hint'.

### 2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of eladocagene exuparvovec finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons

consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

These arise from the conditions attached to the marketing authorisation in exceptional circumstances: a registry of patients with AADC deficiency who have either been treated with eladocagene exuparvovec or not (PTC-AADC-MA-406 (AADCAchieve)). Among other things, data on the long-term efficacy and safety of eladocagene exuparvovec will be collected. In addition to annual interim reports, the final data are expected for the year 2036. Furthermore, final data for the long-term follow-up study AADC-1602 are expected in 2030, again with annual interim reports. These expected additional data are classified as relevant for the benefit assessment and are to be submitted after the end of the time limit.

For this purpose, the G-BA considers a limitation of 5 years for the resolution, until 15 February 2028, to be appropriate.

Even if the final data cannot be presented at this point, it is considered appropriate to reassess the new data at this time.

For the new benefit assessment after expiry of the deadline, the results from the respective interim analyses on all patient-relevant endpoints, in particular also on the motor milestones "standing with support" and "walking with assistance", which are used to demonstrate the extent of additional benefit, from the studies AADC-MA-406 and AADC-1602 are to be submitted in the dossier.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, No. 7 VerfO, the procedure for the benefit assessment of the medicinal product eladocagene exuparvovec recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of eladocagene exuparvovec (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that there is a non-quantifiable additional benefit because the required evidence is not complete.

The possibility that a benefit assessment for the medicinal product eladocagene exuparvovec can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1, paragraph 2, nos. 2 to 4 VerfO) remains unaffected hereof.

### 2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Upstaza" with the active ingredient eladocagene exuparvovec. Upstaza was approved as an orphan drug and under special conditions 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. For eladocagene exuparvovec 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, results of the single-arm long-term follow-up study AADC-1602 are available on the endpoints of mortality, morbidity and side effects. In addition, a non-adjusted indirect comparison without a bridge comparator was presented for the endpoints mortality and the morbidity endpoint "achievement of motor milestones". For this purpose, the pharmaceutical

company compares the data of the long-term follow-up study AADC-1602 (data cut-off 15 July 2022) with a natural history cohort (NHDB).

The indirect comparison presented could not be used due to the described limitations.

Even if the indirect comparison cannot be used for the benefit assessment, the NHDB documents a deterministic natural course of the disease in children with AADC deficiency, in which the motor milestones are not reached by the vast majority of patients. Therefore, the dramatic effects shown in the long-term follow-up study AADC-1602 can be considered in the milestone analyses for the benefit assessment and advantages of eladocagene exuparvovec can be derived with reasonable certainty for the endpoints "achieving full head control" and "sitting unassisted" compared to natural disease progression.

In the absence of robust data for a comparative assessment, it is not possible to quantify the magnitude of the additional benefit based on the data presented.

In addition, due to missing data on quality of life and missing comparative data on mortality and the safety profile of eladocagene exuparvovec, there are relevant uncertainties that do not allow an assessment of the magnitude of the additional benefit. The risk of bias of the single-arm study data is estimated to be high at study and endpoint level.

Overall, a hint for a non-quantifiable additional benefit is derived for eladocagene exuparvovec because the scientific data basis does not allow quantification.

## 2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier. When calculating the lower limit of the range, the pharmaceutical company implicitly assumes a complete coverage of the clinical picture in Germany. This is not comprehensible. Therefore, the lower limit can be assumed to be an underestimate. The upper limit of the range is plausible.

## 2.3 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.

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.

## 2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2023).

Eladocagene exuparvovec is listed in the LAUER-TAXE®, but is only dispensed as a clinic pack.[3] Accordingly, the active ingredient is not subject to the Pharmaceutical Price Ordinance (Arzneimittelpreisverordnung) and no rebates according to Section 130 or Section 130a SGB V apply. The calculation is based on the purchase price of the clinic pack plus 19% value added tax, in deviation from the LAUER-TAXE® data usually taken into account.

[3] Inpatient application is assumed.

To calculate the treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack plus value added tax.

Eladocagene exuparvovec is intended for single bilateral intraputaminal infusion during a surgical session into two areas per putamen. Patients receive a total dose of $1.8 \times 10^{11}$ vector genomes (Vg) as four (two per putamen) 0.08 ml infusions ($0.45 \times 10^{11}$ Vg). Each vial contains $2.8 \times 10^{11}$ Vg of eladocagene exuparvovec in 0.5 ml extractable solution.

Treatment period:

| Designation of the therapy | Treatment mode | Number of treatments/ patient/ year | Treatment duration/ treatment (days) | Treatment days/ patient/ year |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Eladocagene exuparvovec | Single dose; 2 x infusions per putamen | 1 | 1 | 1 |

Consumption:

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| Medicinal product to be assessed | | | | | |
| Eladocagene exuparvovec | 4 x $0.45 \times 10^{11}$ Vector genome (Vg) | 4 x $0.45 \times 10^{11}$ Vg | 1 x $2.8 \times 10^{11}$ Vg | 1 | 1 x $2.8 \times 10^{11}$ Vg |

Costs:

**Costs of the medicinal products:**

| Designation of the therapy | Packaging size | Costs (purchase price clinic pack plus value added tax) | Value added tax (19 %) | Costs of the medicinal product |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Eladocagene exuparvovec $2.8 \times 10^{11}$ Vg | 1 INF | € 3,500,000 | € 665,000 | € 4,165,000 |
| Abbreviations: INF = infusion solution, Vg = vector genome | | | | |

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Eladocagene exuparvovec is administered as an inpatient by bilateral intraputaminal infusion in sites specialised in stereotactic neurosurgery. The basis for calculation for the inpatient costs is the valuation ratio of DRG B20A (8.4) multiplied by the federal base case value 2022 (€ 3,833.07). Furthermore, the nursing revenue is included in the inpatient costs. This is calculated from the average length of stay of DRG B20A (8.4 days) multiplied by the nursing fee Section 15 para. 2A KHEntgG (Act on Fees for Full and Semi-inpatient Hospital Services) (since July 2022: € 200) and the nursing revenue valuation ratio (1.6902).

The calculation of the costs of the invasive treatment method is standardised in the following on the basis of the DRG case flat fee catalogue 2022 and the nursing revenue catalogue 2022, the base rate value of the year 2022 as well as the nursing fee value pursuant to Section 15 paragraph 2a (Act on Charges for Fully and Partially Inpatient Hospital Services), since the federal base rate value for the year 2023 was not yet available at the time of the cost calculation.

| Calculation year | DRG | Average duration of stay | DRG valuation ratio (main department) | Federal base case value | Nursing revenue valuation ratio | Nursing fee | Case flat fee revenue | Nursing revenue | Total case flat fee revenue and nursing revenue |
|---|---|---|---|---|---|---|---|---|---|
| 2022 | B20A | 8.4 | 2.717 | € 3,833.07 | 1.6902 | € 200 | € 10,414.45 | € 2,839.54 | € 13,253.99 |

| Designation of the therapy | Designation of the service | Number | Unit cost | Costs per patient |
|---|---|---|---|---|
| Medicinal product to be assessed | | | | |
| Eladocagene exuparvovec | Intraputaminal infusion of a novel therapy medicinal product with international marketing authorisation [4,5] (Operation and Procedure Codes (OPC): 5-014.8) or 5-936.1) + nursing revenue | 1 | approx. € 13,253.99 | approx. € 13,253.99 |

[4] The costs of intraputaminal infusion are based on inpatient treatment and billing via DRG code B20A.
[5] Shown are the costs for an inpatient procedure.

### 2.5 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

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

## 3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

## 4. Process sequence

On 15 August 2022, the pharmaceutical company submitted a dossier for the benefit assessment of eladocagene exuparvovec to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 November 2022 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 6 December 2022.

The oral hearing was held on 19 December 2022.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 18 January 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 24 January 2023, and the proposed resolution was approved.

At its session on 2 February 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal products | 8 November 2022 | Information of the benefit assessment of the G-BA |
| Working group Section 35a | 14 December 2022 | Information on written statements received; preparation of the oral hearing |
| Subcommittee Medicinal products | 19 December 2022 | Conduct of the oral hearing |
| Working group Section 35a | 4 January 2023<br>18 January 2023 | Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure |
| Subcommittee Medicinal products | 24 January 2023 | Concluding discussion of the draft resolution |
| Plenum | 2 February 2023 | Adoption of the resolution on the amendment of Annex XII AM-RL |

Berlin, 2 February 2023

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

Prof. Hecken