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)
Vosoritide (new therapeutic indication: achondroplasia, ≥ 4 months to < 2 years)

of 16 May 2024

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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient vosoritide (Voxzogo) was listed for the first time on 1 October 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

Voxzogo is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

Within the previously approved therapeutic indications, the sales volume of vosoritide with the statutory health insurance at pharmacy sales prices, including value-added tax exceeded € 30 million. Evidence must therefore be provided for vosoritide in accordance with Section 5, paragraph 1 through 6 of the G-BA's Rules of Procedure (VerfO), and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 25 October 2023, vosoritide received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008

concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 22 November 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) on the active ingredient vosoritide with the new therapeutic indication "Voxzogo is indicated for the treatment of achondroplasia in patients 4 months of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing." in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 March 2024 on the G-BA website (www.g-ba.de), therefore initiating the written statement procedure. In addition, an oral hearing was held.

Based on the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure, the G-BA decided on the question on whether an additional benefit of secukinumab compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by IQWiG according to the General Methods was not used in the benefit assessment of nivolumab – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Vosoritide (Voxzogo) according to product information

Voxzogo is indicated for the treatment of achondroplasia in patients 4 months of age and older whose epiphyses are not closed. The diagnosis of achondroplasia should be confirmed by appropriate genetic testing.

Therapeutic indication of the resolution (resolution of 16.05.2024):

Voxzogo is indicated for the treatment of achondroplasia in patients from 4 months to < 2 years of age and older whose epiphyses are not closed.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients 4 months to < 2 years of age with achondroplasia and whose epiphyses are not closed

Appropriate comparator therapy:

Best supportive care

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or

3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

on 1. Apart from the medicinal product to be assessed, no other medicinal products are specifically approved for the treatment of achondroplasia.

on 2. Non-medicinal treatments as part of the appropriate comparator therapy are not considered in the present therapeutic indication.

on 3. The following resolutions of the G-BA on the benefit assessment according to Section 35a SGB V are available for the present therapeutic indication:

- Vosoritide (resolution of 15 February 2024)

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

The evidence in the present therapeutic indication is limited overall. In an update of the S1 guideline on "short stature"[1] of 6 March 2023, the active ingredient vosoritide to be assessed is mentioned as the only treatment option for achondroplasia, and support from a paediatrician or paediatric endocrinologist or, in individual cases, paediatric psychological support is recommended. As part of the previous written statement procedure on the active ingredient vosoritide for the treatment of achondroplasia in children 2 years of age and older, the AkDÄ stated that there is no targeted medicinal therapy for subjects with achondroplasia. The treatment of patients is primarily supportive, including the administration of analgesics as required, the treatment of complications and the provision of aids.

Against this background, the G-BA determined best supportive care as an appropriate comparator therapy for vosoritide for children with achondroplasia 4 months to < 2 years of age, whose epiphyses are still open. "Best supportive care" (BSC) is understood as the therapy

1 Binder G, Woelfle J. Kleinwuchs; Update for r S1 guideline no. 174-004. Available online at: https://register.awmf.org/assets/guidelines/174-004l_S1_Kleinwuchs_2023-07.pdf (last revised 10.01.2024)

that ensures the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

Hint for a non-quantifiable additional benefit

Justification:

For the assessment of the additional benefit of vosoritide compared with the appropriate comparator therapy of best supportive care, the pharmaceutical company presented the randomised, controlled BMN 111-206 study (206) and its open-label extension study BNM 111-208 (208).

Study 206

Study 206 is a randomised phase, double-blind phase II study comparing vosoritide versus placebo in children 0 to < 5 years of age with genetically confirmed achondroplasia over 52 weeks.

The study population comprises 3 cohorts:

- Cohort 1: Children aged ≥ 2 to < 5 years,
- Cohort 2: Children aged ≥ 6 months to < 2 years and
- Cohort 3: Children aged 0 to < 6 months.

However, as the therapeutic indication to be assessed only includes children 4 months to < 2 years of age, only the data from cohorts 2 and 3 are analysed.

The sub-population of study 206 relevant for the benefit assessment consisted of 8 (Cohort 2) and 9 children (Cohort 3) in the intervention arm and 8 children in each of the comparator arms. The relevant sub-population thus comprises a total of 33 children. This corresponds to approx. 51.6% of the total study population of study 206. Where possible and appropriate, cohorts 2 and 3 are summarised meta-analytically.

The children 0 months of age and older included in cohort 3 received their 1st dose of Vosoritide at the earliest at the age of 4 months due to the required observation phase. . Patients in cohorts 2 and 3 were generally treated with 30 µg/kg vosoritide subcutaneously once daily or with placebo subcutaneously once daily in accordance with the marketing authorisation. In addition to the study medication, concomitant treatments were permitted at the discretion of the principal investigator. Overall, adequate implementation of the appropriate comparator therapy BSC in study 206 is assumed.

The primary endpoint of the study 206 was the change in body length/ height z-score as well as safety and tolerability. Other patient-relevant endpoints were assessed in the categories of mortality and morbidity.

208 study (long-term data):

Children who completed the placebo-controlled study 206 subsequently had the opportunity to take part in the open-label extension study 208 and continue treatment with vosoritide. A total of 73 patients were enrolled into one of 4 age cohorts (age at 1st administration of vosoritide: 0 to < 6 months, ≥ 6 to < 24 months, ≥ 24 to < 60 months, ≥ 60 months). Observation continues until the child reaches almost final adult height. This is defined as proof of closure of the growth plates and an annual growth rate < 1.5 cm per year. For the ongoing study 208, the pharmaceutical company submits data for the endpoints of height (z-score), annual growth rate and ratio of upper to lower body segment.

However, the long-term data from study 208 are currently inadequate to assess the long-term effect of vosoritide with early treatment initiation (less than 2 years). There is currently only limited data over a period of 3.5 years (maximum significant period: Cohort 2 = 3.5 years; Cohort 3 = 2 years) for up to 23 patients, which do not allow any clear conclusions to be drawn.

Extent and probability of the additional benefit

Mortality

Overall mortality was collected as part of the adverse events. There were no deaths in cohort 2 of the study 206. In the cohort 3, there was no statistically significant difference between the treatment groups.

Morbidity

Body height (z score)

Height (z score) is classified as patient-relevant in the present therapeutic indication of achondroplasia.

Z-scores for body height are derived using age and sex-specific reference data for children of average stature. The data were presented as z-scores (number of standard deviations) above or below the age-specific reference. The reference corresponds to a z-score of 0. Short stature is defined as a height deficit of at least 2.0 standard deviations below the population-specific mean height for age and sex, corresponding to a z-score of -2. In the study 206, a US reference population (CDC) was used to calculate height z-scores.

For the endpoint "body height" (z-score), there was no statistically significant difference between the treatment groups in the meta-analysis of cohorts 2 and 3 of study 206.

Annualized growth rate

For the present benefit assessment, the endpoint of body height (z-score) is used. Since an increased annual growth rate results directly in an increase in height, this is adequately covered by the endpoint of body height (z-score). The annual growth rate is therefore presented additionally.

For the endpoint of annualized growth rate, there was no statistically significant difference between the treatment groups in the meta-analysis of cohorts 2 and 3 of study 206.

Ratio of upper to lower body segment and body proportions of the extremities

Achondroplasia is characterised by disproportionate short stature. The endpoints "ratio of upper to lower body segment" and "body proportions of the extremities" are therefore considered patient-relevant in this therapeutic indication of achondroplasia. However, changes in the ratio of body proportions should also be reflected in other patient-relevant endpoints such as functional limitations and mobility.

However, the operationalisation of the endpoints ratio of upper to lower body segment and body proportions presented in the dossier does not allow an assessment of a patient-relevant change in disproportionality, as only the change compared to baseline was analysed. A comparison of body proportions with a suitable healthy reference population was not presented. Therefore, the endpoints are only presented additionally.

No suitable data is available for the endpoints "ratio of upper to lower body segment" and "body proportions of the extremities".

Functional independence (WeeFIM)

The WeeFIM is an instrument for assessing the functional independence of children (6 months to 7 years) with developmental disorders or special care needs from the perspective of parents or caregivers. The instrument consists of 18 items, which are assigned to the 3 domains of self-care, mobility and cognition. An overall score is also calculated. The instrument queries the current time. In Study 206, the endpoint was recorded at screening, week 26, week 52 and at premature study discontinuation.

In Study 206, the WeeFIM was only collected from the age of 6 months. For cohort 3 (children 0 to < 6 months), no suitable data are therefore available to assess functional independence. For cohort 2 (children ≥ 6 months to < 2 years), there was no statistically significant difference between the treatment groups in the endpoint of functional independence, either in the overall score or in the individual domains.

Quality of life

Infant and Toddler Quality of Life Questionnaire (ITQoL)

The ITQoL is a parent-reported instrument that is used with infants and toddlers aged 2 months to 5 years. The total of 97 items are summarised into 13 subscales, 10 of which cover the child's general health. The ITQoL uses the 3 additional subscales to record parental effects that are not directly patient-relevant and are therefore not used to assess the additional benefit. The subscales of behaviour, overall behaviour, getting along with others and change in health are only surveyed from the age of ≥ 12 months. Thus, no suitable data are available for cohort 3 (children 0 to < 6 months) of study 206 due to the lack of a baseline survey. In cohort 2, there are also no baseline surveys available for patients aged ≥ 6 to ≤ 12 months at the start of study. As it is not possible to adequately assess on the basis of the available information whether the criteria regarding the percentage of patients included in the analysis as a whole or regarding the difference in the percentage of patients between the treatment groups included in the analysis are met, no suitable data are available for these subscales for

Cohort 2 of the study 206. In addition, no suitable data are available for the general health subscale, which can be surveyed from 2 months according to the instrument, due to the large difference between the treatment groups (> 15 percentage points) with regard to the percentage of patients who were not included in the evaluation.

In the overall assessment, this means that no suitable data for deriving an additional benefit are available for the health-related quality of life assessed using ITQoL.

Side effects

For the endpoint of serious AEs (SAEs), there was no statistically significant difference between the treatment groups in the meta-analysis of cohorts 2 and 3 of study 206.

There were no events in Cohort 2 of the study 206 for the endpoint of severe AEs. In the cohort 3, there was no statistically significant difference between the treatment groups.

For the endpoint of discontinuation due to AEs, there were no events in either cohort 2 or cohort 3 of the study 206.

The meta-analysis of cohorts 2 and 3 of the study 206 showed a statistically significant disadvantage of vosoritide compared to BSC for the endpoint of reactions at the injection site (AEs).

Assessment with regard to transfer of additional benefit

For the present therapeutic indication of the treatment of achondroplasia in children from 4 months to < 2 years of age, a direct comparator study over a period of 52 weeks is available in which vosoritide is compared with BSC (study 206). However, only cohorts 2 and 3 of the study 206 are relevant for the patient population to be assessed. Overall, therefore, only direct comparator data is available for 33 children 4 months to < 2 years of age. The direct comparator evidence for this patient population must therefore be considered limited.

The assessment report of the European Medicines Agency (EMA) on the active ingredient vosoritide (Voxzogo)[2] states that the extrapolation of the data on the efficacy of vosoritide from children ≥ 2 years to children < 2 years of age is considered possible due to the same pathophysiology of achondroplasia. In addition, there is no evidence that the pharmacology of vosoritide in children < 2 years differs from that in children ≥ 2 years of age. Furthermore, it is mentioned that despite the lack of statistical effects for the population of children < 2 years of age, the increase in terms of standard deviation to total body size in the first year of treatment appears similar. Furthermore, it can be assumed that the influence of vosoritide on body growth and body proportions is greater the earlier the therapy is started in childhood.

The EMA's findings on the medical rationale are also decisive for the G-BA to consider the evidence for children older than 2 years in addition to the direct comparator evidence for children 4 months to < 2 years of age.

2 European Medicines Agency. Voxzogo; Assessment report - Variation [online]. 2023 [accessed: 22.04.2024]. URL: https://www.ema.europa.eu/en/documents/variation-report/voxzogo-h-c-005475-ii-0006-epar-assessment-report-variation_en.pdf

The appropriate comparator therapy defined by the G-BA for children < 2 years of age is identical to the appropriate comparator therapy for children and adolescents ≥ 2 years of age. BSC is the appropriate comparator therapy for all patients with achondroplasia whose epiphyses are not closed. In this respect, this is also a decisive criterion for the transfer of evidence of patients ≥ 2 years of age with achondroplasia in the context of the present benefit assessment.

Overall assessment

The present benefit assessment is based on the results of Cohort 2 (children aged ≥ 6 months to < 2 years) and Cohort 3 (children aged 0 to < 6 months) of the double-blind, controlled, multicentre study 206, in which vosoritide vs placebo was investigated over a period of 52 weeks, in each case in addition to BSC. In contrast, the long-term data submitted from study 208 are currently inadequate to assess the long-term effect of vosoritide with early treatment initiation (less than 2 years).

There were no deaths in cohort 2 of the study 206. In the Cohort 3 study, there was no statistically significant difference between the treatment groups.

In the endpoint categories of morbidity and side effects, there were no statistically significant differences between the two treatment arms.

No suitable data are available for the endpoint category of quality of life.

In summary, based on the results from the study 206, there were no statistically significant differences for children 4 months to < 2 years of age compared to BSC.

Overall, the available evidence based on the results of the study 206 for the age group of children ≥ 4 months to < 2 years includes only a few patients (vosoritide: 17 vs placebo: 16) and is therefore limited. Based on the results of Cohorts 2 and 3 of the study 206 described above, there were no statistically significant differences between treatment with vosoritide compared to BSC. Due to the comparable pathophysiology of the disease throughout childhood and the medical rationale that the influence of vosoritide on body growth and body proportions is greater the earlier therapy is started in childhood, the results of older patients ≥ 2 years of age are also taken into account for the present assessment and the evidence is transferred to children aged ≥ 4 months to < 2 years.

In the benefit assessment of vosoritide for patients with achondroplasia ≥ 2 years of age whose epiphyses are not closed, an indication of a non-quantifiable additional benefit was identified (resolution of 15 February 2024). This is based on a statistically significant advantage for the endpoint "body height (z-score)" of vosoritide compared with the appropriate comparator therapy in the meta-analytic summary of Cohort 1 of the study 206 and study 301. Children aged ≥ 2 to < 5 years (study 206) grew on average 0.96 cm more with vosoritide treatment than in the placebo arm over the study duration of 52 weeks. The difference was 1.57 cm in subjects aged ≥ 5 years in study 301. The supporting evaluations of the long-term data in this procedure also suggested that the positive effect of vosoritide on the endpoint of body height (z-score) is sustained. However, the extent of the additional benefit could not be quantified, as it was not possible to conclusively assess how the improvement in body height affects the complications and functional impairment associated with achondroplasia. In addition, there is a lack of long-term evaluations up to the end of the epiphyseal plates to

assess the final size achieved under vosoritide treatment. Based on Cohort 1 of study 206 and study 301, there were no statistically significant differences between the treatment groups in the other endpoint categories.

In the overall assessment, with reference to the results of the study 206 (Cohort 1) and study 301 in patients ≥ 2 years of age, an additional benefit of vosoritide over BSC was established for children from 4 months to < 2 years of age with achondroplasia whose epiphyses are not closed. However, the extent of the additional benefit cannot be quantified due to the limited evidence available.

Reliability of data (probability of additional benefit)

Due to the uncertainty caused by the transfer of the results from an older patient population to the younger patient population to be assessed here, a hint for a non-quantifiable additional benefit can be identified.

2.1.4 Summary of the assessment

The present benefit assessment is the benefit assessment of a new therapeutic indication for the active ingredient vosoritide. The therapeutic indication assessed here comprises the treatment of achondroplasia in children ≥ 4 months to < 2 years of age whose epiphyses are not yet closed. The G-BA determined Best Supportive Care (BSC) to be the appropriate comparator therapy.

For this patient group, the pharmaceutical company is presenting the results of the randomised, controlled BMN 111-206 study, in which vosoritide is being investigated vs placebo over a period of 52 weeks in addition to BSC. The presented long-term data of the BMN 111-208 study are currently inadequate to assess the long-term effect of vosoritide with early treatment initiation (less than 2 years).

In the endpoint categories of morbidity and side effects, there were no statistically significant differences between the two treatment arms.

No suitable data are available for the endpoint category of quality of life.

In summary, based on the results from the BMN 111-206 study for children 4 months to < 2 years of age, there were no statistically significant differences between vosoritide and BSC.

For the patient population to be assessed, children 4 months to < 2 years of age, only direct comparator data for 33 children are available. The evidence for this patient population is therefore considered limited. Due to the comparable pathophysiology of the disease throughout childhood and the medical rationale that the influence of vosoritide on body growth and body proportions is greater the earlier therapy is started in childhood, the results of older patients ≥ 2 years of age are also taken into account and the evidence is transferred to children aged ≥ 4 months to < 2 years.

For patients ≥ 2 years of age with achondroplasia, a statistically significant advantage was shown for vosoritide over the appropriate comparator therapy for the endpoint "body height (z-score)". Supporting evaluations of long-term data also suggested that the positive effect of vosoritide on the body height endpoint (z-score) is sustained.

In the overall assessment, the G-BA therefore identified a hint for a non-quantifiable additional benefit for vosoritide in children 4 months to < 2 years of age with achondroplasia compared with the appropriate comparator therapy BSC, taking into account the results of patients ≥ 2 years of age.

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 resolution is based on the information from the dossier assessment of the IQWiG (A23-116).

From the information provided by the pharmaceutical company on the age group from 4 months and from the information on the age group from 2 years (389 [327-461] patients), the difference for the SHI target population is 41 (35-49) patients 4 months to < 2 years of age. These figures tend to be overestimated in the lower limit because the patient numbers may be lower if the prevalence of achondroplasia is taken into account on the basis of live births only.

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 Voxzogo (active ingredient: vosoritide) at the following publicly accessible link (last access: 2 April 2024):

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

Treatment with vosoritide must only be initiated and monitored by doctors experienced in the treatment of patients with growth disorders or skeletal dysplasias.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 May 2024).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

The treatment costs for best supportive care are different from patient to patient. Because best supportive care has been determined as an appropriate comparator therapy, this is also reflected in the medicinal product to be assessed. The type and scope of best supportive care can vary depending on the medicinal product to be assessed and the comparator therapy.

Treatment period:

Patients 4 months to < 2 years of age with achondroplasia and whose epiphyses are not closed

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Vosoritide	Continuously, 1 x daily	365	1	365
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care				
Best supportive care	Different from patient to patient			

Consumption:

For calculating the dosing range depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight of a child < 2 years of age = 11.6 kg)[3].

Since vosoritide can be stored only for a maximum of 3 hours after reconstitution, discarding must be taken into account, consequently the consumption per injection is presented.

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					
Vosoritide children ≥ 4 kg to < 5 kg	0.12 mg	0.12 mg	1 x 0.4 mg	365.0	365 x 0.4 mg
Vosoritide children ≥ 5 kg to < 6 kg	0.16 mg	0.16 mg	1 x 0.4 mg	365.0	365 x 0.4 mg
Vosoritide Children ≥ 6 kg to < 8 kg	0.2 mg	0.2 mg	1 x 0.4 mg	365.0	365 x 0.4 mg
Vosoritide children ≥ 8 kg to < 12 kg	0.24 mg	0.24 mg	1 x 0.4 mg	365.0	365 x 0.4 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care					
Best supportive care	Different from patient to patient				

3 Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual 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 after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Vosoritide 0.4 mg	10 PSI	€ 6,556.16	€ 2.00	€ 371.13	€ 6,183.03
Best supportive care	Different from patient to patient				
Abbreviations: PSI = powder and solvent for solution for injection					

LAUER-TAXE® last revised: 1 May 2024

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.

Because there are no 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, no costs for additionally required SHI services need to be taken into account.

2.5 Designation of 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 the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1

SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Patients 4 months to < 2 years of age with achondroplasia and whose epiphyses are not closed

- No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

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

At its session on 10 October 2023, the Subcommittee on Medicinal Products determined the appropriate comparator therapy after issuing the positive opinion.

On 22 November 2023, the pharmaceutical company submitted a dossier for the benefit assessment of vosoritide to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 28 November 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient vosoritide.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 1 March 2024. The deadline for submitting statements was 22 March 2024.

The oral hearing was held on 8 April 2024.

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 7 May 2024, and the proposed resolution was approved.

At its session on 16 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 October 2023	Implementation of the appropriate comparator therapy
Working group Section 35a	3 April 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	8 April 2024	Conduct of the oral hearing
Working group Section 35a	16 April 2024 29 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	7 May 2024	Concluding discussion of the draft resolution
Plenum	16 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 16 May 2024

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

Prof. Hecken