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 and Annex XIIa – Combinations of Medicinal Products with New Active Ingredients according to Section 35a SGB V Vosoritide (reassessment due to exceeding the € 30 million turnover limit: achondroplasia, ≥ 2 years)

of 15 February 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® for the treatment of achondroplasia in patients 2 years and older 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.

At its session on 18 March 2022, the G-BA decided on the benefit assessment of vosoritide in the therapeutic indication "Treatment of achondroplasia in patients 2 years and older" according to Section 35a SGB V.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Section 5, paragraphs 1 to 6 within three months of being

requested to do so by the Federal Joint Committee, and in this evidence must demonstrate the additional benefit compared to the appropriate comparator therapy.

By letter dated 5 December 2022, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 September 2023, due to exceeding the € 30 million turnover limit within the period from 1 December 2021 to 30 November 2022. The pharmaceutical company has 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 6 VerfO on 01 September 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 1 December 2023 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of vosoritide compared with the appropriate comparator therapy could be determined on the basis of 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, as well of the addendum drawn up by the IQWiG on the benefit assessment. 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 the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of vosoritide.

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 15.02.2024):

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

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients 2 years of age and older with achondroplasia and whose epiphyses are not closed

Appropriate comparator therapy for vosoritide:

- 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:

1st 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. There are no resolutions of the G-BA for the therapeutic indication of achondroplasia.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as 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 a recent update of the S1 guideline on "short stature"[2], the only treatment option mentioned was the active ingredient vosoritide to be assessed here, and support from a paediatrician or paediatric endocrinologist or, in individual cases, paediatric psychological support was recommended. The AkDÄ also explained during the written statement procedure 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. Limb-lengthening operations are only performed in Germany in individual cases.

Against this background, the G-BA determined best supportive care as an appropriate comparator therapy for vosoritide for children aged 2 years and older, adolescents and adults with achondroplasia whose epiphyses are still open. "Best supportive care" (BSC) is understood as the therapy 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 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)

2.1.3 Extent and probability of the additional benefit

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

For patients with achondroplasia aged 2 years and older in whom the epiphyses are not yet closed, there is an indication of a non-quantifiable additional benefit for vosoritide.

Justification:

For the benefit assessment, the pharmaceutical company presented the randomised controlled trials (RCTs) BMN 111-206 and BMN 111-301 (hereinafter referred to as studies 206 and 301) as well as various evaluations to illustrate the long-term effects of treatment with vosoritide in the dossier. To illustrate the long-term effects of treatment with vosoritide, the pharmaceutical company presents results on selected endpoints in the dossier over the periods of the RCTs and their extension studies (301/302 and 206/208), over the period of the BMN 111-202 (202) and BMN 111-205 (205) studies and over the period of the observational study BMN 111-901 (901) of at least 1 year, the RCT 301 and the 1st treatment year of the extension study 302.

Study 206

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

The study population comprises 3 cohorts: Cohort 1 aged 2 to < 5 years, cohort 2 from 6 months to < 2 years and cohort 3 under 6 months. However, as the present therapeutic indication only includes patients aged 2 years and older, only the available study characteristics and data from cohort 1 are considered. The relevant sub-population of the study 206 consisted of 15 patients in the intervention arm and 16 in the comparator arm.

In the intervention arm, the patients received vosoritide subcutaneously once a day in compliance with the marketing authorisation, while the comparator arm was treated with placebo. 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. Following study 206, all suitable patients had the opportunity to continue treatment with vosoritide in the open-label extension study 208.

Study 301

Study 301 is a double-blind, randomised phase III study over 52 weeks comparing vosoritide versus placebo in children and adolescents aged 5 to < 18 years with genetically confirmed achondroplasia.

The prerequisite for enrolment in the study was an annualized growth rate of at least 1.5 cm per year and that the epiphyses were not yet closed.

In the study 301, a total of 60 patients were randomised to the intervention arm and 61 patients to the comparator arm. All of the subjects enrolled were under 15 years old.

In the intervention arm, patients received vosoritide subcutaneously once daily in compliance with the marketing authorisation; in the comparator arm, treatment was carried out with placebo. 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 301 is assumed.

The primary endpoint of the study 301 was the change in annualized growth rate. Other patient-relevant endpoints were assessed in the categories of mortality, morbidity, health-related quality of life and side effects. Following study 301, all patients had the opportunity to continue treatment with vosoritide in the ongoing open-label extension study 302.

Meta-analytic summary of the results

For the present benefit assessment, the meta-analytically summarised results of the studies 206 and 301 were used, if available.

Despite different and non-overlapping age groups in the two studies, the meta-analysis is supported, among other things, by the consideration of the subgroup analyses on age at the start of study for the age-adjusted endpoint of body height (z-score), which is relevant in the present assessment, and that the study populations do not differ significantly except for age.

Long-term data

In order to be able to assess the sustainability of the effects of vosoritide from studies 206 and 301, partial results of the long-term data presented by the pharmaceutical company were considered in support of the present benefit assessment. These include evaluations of changes from baseline from RCTs and their extension studies 202/205, 206/208 and 301/302 and a 2-year comparison of vosoritide therapy versus placebo from studies 901/301/302.

Study 202 is a sequential open-label phase II dose escalation study with a subsequent extension study 205. Study 901 is a prospective observational study to collect baseline growth measurements in patients who were eligible for subsequent intervention studies (study 202, 206 or 301).

Extent and probability of the additional benefit

Mortality

Overall mortality was collected as part of the adverse events. There were no deaths in studies 206 and 301.

Morbidity

Body height (z score)

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

Body height was recorded as standing height (not length) as well as age and sex-adjusted z scores were calculated. The z scores reflect the number of standard deviations (SD) of each

score from the normal mean scores, standardised by age and sex. The data were presented as SD values above or below the age-specific reference (≙ 0).

In study 206 and study 301, a US reference population was used to calculate the z-score. In addition, post hoc evaluations of a German reference population for study 301 are available in order to assess the transferability of the results to the German healthcare context.

At baseline, the children and adolescents had a lower body height than the selected reference population. The meta-analysis of the studies 206 and 301 for the endpoint of body height as a z-score in relation to the American reference population shows a significant improvement in body height with vosoritide compared to placebo. 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 analysis of the long-term data from studies 901/301/302 (2-year comparison versus placebo), 206/208 (up to 2.5 years, comparison versus baseline), 301/302 (up to 3.5 years, comparison versus baseline) and 202/205 (up to 7 years, comparison versus baseline) shows that the effect on the endpoint of body height (z-score) is sustained and does not call into question the results of the meta-analysis of studies 206 and 301 with regard to the benefit of vosoritide.

Furthermore, it is assumed that the results of the meta-analysis are transferable to the German healthcare context, as the respective group difference in study 301 does not differ significantly when using the German or the American reference population.

Annualized growth rate

The endpoint of growth rate describes the annual increase in standing height [cm/ year] and is only presented additionally, as it does not provide any information on growth other than height for the benefit assessment.

The meta-analytic summary of the studies 206 and 301 showed a statistically significant increase in the annualized growth rate related to 1 year in favour of vosoritide compared to the control group.

Ratio of upper to lower body segment and ratio of body proportions

Achondroplasia is characterised by disproportionate short stature. The endpoints "ratio of upper to lower body segment" and "ratio of body proportions" are therefore considered patient-relevant in the present therapeutic indication. 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 data are only presented additionally.

The data from the observational study 901 show that patients in RCTs 206 and 301 were already disproportionate in terms of upper and lower body segments or extremities at the start of study.

After 52 weeks of treatment, the meta-analysis of studies 206 and 301 showed no statistically significant differences between the treatment groups.

Functional independence (WeeFIM)

The WeeFIM is an instrument for assessing the functional independence of children aged 6 months to 7 years with developmental disorders or special care needs from the perspective of parents or caregivers.

The WeeFIM was collected in both studies (206 and 301). For the study 301, only one evaluation is available for the entire study population, which also enrolled children and adolescents over the age of 7. As the validity of the instrument is only proven for children up to the age of 7 years, the results are not considered for the present benefit assessment.

In the study 206, there was no difference was determined between the treatment groups for the endpoint of functional independence.

Quality of life

Health-related quality of life was assessed in the study 301 using a generic instrument - the Paediatric Quality of Life Inventory (PedsQL) - and a disease-specific instrument - the Quality of Life in Short Stature Youth (QoLISSY). The Infant and Toddler Quality of Life Questionnaire (ITQoL) was used in the study 206.

QoLISSY and PedsQL

The QoLISSY questionnaire is an instrument for assessing the quality of life of children and adolescents with short stature. However, individual domains such as "coping" and "beliefs" are only predictors of health-related quality of life and are therefore categorised as morbidity.

The PedsQL is a generic instrument for measuring health-related quality of life, which includes four dimensions (physical, emotional, social and school functioning).

For both questionnaires, there are versions for direct questioning of children and adolescents (from the age of 8) and versions for questioning the parents of affected children and adolescents (from the age of 4).

In the study 301, both the parent-reported and the patient-reported versions of the quality of life questionnaires were collected. As the health-related quality of life for patients aged 8 to < 18 years is adequately represented by the patient-reported survey relevant for the benefit assessment, the evaluations of the parent-reported versions of the instrument are only used for children aged 5 to < 8 years.

There were no statistically significant differences between vosoritide + BSC and BSC for the health-related quality of life measured using the disease-specific quality of life questionnaire QoLISSY and the generic instrument PedsQL in study 301.

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 other 3 subscales measure the impact on the parents and family of the children, which are not directly patient-relevant and are therefore not used for the present benefit assessment.

For the endpoint of health-related quality of life, assessed with the ITQoL in the study 206, there were no significant differences between the treatment groups overall.

However, no suitable data is available for the "getting along with others" subscale due to excessive differences between the treatment arms in the number of subjects evaluated, and there are uncertainties as to whether the results for this subscale of the ITQoL were transformed appropriately.

Side effects

In study 206, no events occurred in the endpoints of severe AEs and therapy discontinuation due to AEs. There were no significant differences between the treatment groups for the severe AEs and therapy discontinuation due to AEs.

For the endpoint of serious AEs (SAEs) and the specific AE "reactions at the injection site", the meta-analysis of the studies 206 and 301 showed no significant difference between the treatment groups.

Overall assessment

The benefit assessment is based on the results of the double-blind, controlled, multicentre studies 206 and 301, which investigate the administration of vosoritide versus placebo in children and adolescents with achondroplasia over 52 weeks in each case in addition to BSC (206: 2 to <5 years and 301: 5 to 18 years). For an assessment of the sustainability of the effects of vosoritide, partial results of the long-term data presented in the dossier are considered supportively. In addition to the studies mentioned, these contain data from the studies 901, 202, 205, 208 and 302.

There were no deaths in the studies 206 and 301.

In the endpoint category of morbidity, the meta-analytic summary of the two studies shows a statistically significant advantage of vosoritide over the appropriate comparator therapy for the endpoint "body height (z-score)". The supportively considered evaluations of the long-term data on this endpoint also suggest that the positive effect of vosoritide on growth is maintained over a longer period of time. There is neither an advantage nor a disadvantage for vosoritide in the study 206 for functional impairment assessed using WeeFIM.

With regard to quality of life, measured using Quality of Life in Short Stature Youth (QoLISSY) and PedsQL in study 301 and using ITQoL in study 206, there were no differences between the treatment groups.

There were also no relevant differences between the treatment groups in terms of side effects.

In the overall assessment, an additional benefit of vosoritide was identified for patients with achondroplasia whose epiphyses are not yet closed, based on the advantage in the endpoint "body height (z-score)". However, the extent of the additional benefit cannot be quantified, as it is 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.

Reliability of data (probability of additional benefit)

The benefit assessment of vosoritide for the treatment of achondroplasia in patients aged 2 years and older in whom the epiphyses are not yet closed is based on two randomised controlled trials - 206 and 301, in which vosoritide + BSC is compared with BSC over 52 weeks. For both studies, the risk of bias across endpoints is classified as low, as is the risk of bias of the endpoints. However, the endpoints of functional independence and health-related quality of life, measured using PedsQL and ITQoL, are an exception for which the risk of bias is considered to be high.

There are uncertainties as to how or whether vosoritide treatment affects the disproportionality of body proportions caused by achondroplasia, as no suitable data are available compared to a healthy reference population.

Overall, the reliability of data is categorised as an indication.

2.1.4 Summary of the assessment

The present assessment is the new benefit assessment of the active ingredient vosoritide due to the exceeding of the € 30 million turnover limit. The therapeutic indication assessed here comprises the treatment of achondroplasia in patients 2 years of age and older whose epiphyses are not yet closed. The G-BA determined Best Supportive Care (BSC) to be the appropriate comparator therapy.

The present benefit assessment is based on the results of the double-blind, controlled, multicentre studies BMN-111-206 und -301, which investigated the administration of vosoritide versus placebo in children and adolescents with achondroplasia aged over 52 weeks in each case in addition to BSC (206: 2 to <5 years and 301: 5 to 18 years). For an assessment of the sustainability of the effects of vosoritide, partial results of the long-term data presented in the dossier are considered supportively.

There were no deaths in the studies 206 and 301.

In the endpoint category of morbidity, the meta-analytic summary of the two studies shows a statistically significant advantage of vosoritide over the appropriate comparator therapy for the endpoint "body height (z-score)". The supportively considered evaluations of the long-term data on this endpoint also suggest that the positive effect of vosoritide on growth is maintained over a longer period of time. There is neither an advantage nor a disadvantage for vosoritide in the study 206 for functional impairment.

There were also no differences between the treatment groups in terms of quality of life, assessed using ITQoL, QoLISSY and PedsQL, or in terms of side effects.

Overall, for patients with achondroplasia whose epiphyses are not yet closed, an additional benefit of vosoritide based on the advantage in the endpoint "body height (z-score)" was

identified. However, the extent of the additional benefit cannot be quantified, as it is not possible to conclusively assess how the improvement in body height affects the complications and functional impairment of patients 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.

In addition, there are uncertainties as to how or whether vosoritide treatment affects the disproportionality of body proportions caused by achondroplasia, as no suitable data are available compared to a healthy reference population.

Overall, an indication of non-quantifiable additional benefit is found.

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 (A23-92).

The information provided by the pharmaceutical company on the number of patients with lower limit achondroplasia tends to be overestimated. The main reason for this is that the number of patients 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: 10 January 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: 15 January 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:

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	Children ≥ 2 years			
	Continuously, 1 x daily	365	1	365
	Adolescents < 18 years			
	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 dosage range calculation depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" as well as "Microcensus 2021 – body measurements of the population" were applied (average body weight of a child aged 2 years = 14.1 kg[3] and patients aged < 18 years = 67.2 kg).[4]

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.

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

[4] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment day/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Vosoritide	Children ≥ 2 years				
	0.35 ml = 0.28 mg	0.28 mg	1 x 0.56 mg	365.0	365.0 x 0.56 mg
	Adolescents < 18 years				
	0.35 ml = 0.70 mg	0.70 mg	1 x 1.2 mg	365.0	365.0 x 1.2 mg
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care					
Best supportive care	Different from patient to patient				

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 0.56 mg	10 PSI	€ 6,556.16	€ 2.00	€ 371.13	€ 6,183.03
Vosoritide 1.2 mg	10 PSI	€ 6,556.16	€ 2.00	€ 371.13	€ 6,183.03
Best supportive care	Different from patient to patient				
Appropriate comparator therapy					
Best supportive care	Different from patient to patient				
Abbreviations: PSI = powder and solvent for solution for injection					

LAUER-TAXE® last revised: 15 January 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 2 years of age and older with achondroplasia and whose epiphyses are not closed

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

References:
Product information for vosoritide (Voxzogo); VOXZOGO® 0.4 mg/- 0.56 mg/- 1.2 mg powder and solvent for solution for injection; last revised: October 2023

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 March 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 14 September 2021.

On 1 September 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 6 VerfO.

By letter dated 1 September 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 29 November 2023, and the written statement procedure was initiated with publication on the G-BA website on 1 December 2023. The deadline for submitting statements was 22 December 2023.

The oral hearing was held on 8 January 2024.

By letter dated 10 January 2024, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 26 January 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 6 February 2024, and the proposed resolution was approved.

At its session on 15 February 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	10 March 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	14 September 2021	New implementation of the appropriate comparator therapy
Subcommittee Medicinal products	8 January 2024	Information on written statements received, conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 January 2024 30 January 2024	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	6 February 2024	Concluding discussion of the draft resolution
Plenum	15 February 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 15 February 2024

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

Prof. Hecken