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
Setmelanotide (obesity and control of hunger, POMC, PCSK1 or LEPR-deficiency obesity, ≥ 6 years)

of 1 December 2022

Contents

1. Legal basis

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

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

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

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

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

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

2. Key points of the resolution

The active ingredient setmelanotide is generally excluded from prescription as a slimming agent in accordance with Annex II of the Pharmaceuticals Directive (exclusion from prescription of medicinal products to improve the quality of life in accordance with Section 34, paragraph 1, sentence 7 SGB V, lifestyle medicinal products). However, by resolution of 20 January 2022, amended on 21 April 2022, there is an exemption from the prescription exclusion for setmelanotide in relation to genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above (effective date 30 April 2022). The relevant date for the start of the benefit assessment procedure was 1 June 2022 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA for the first placing on the (German) market of the active ingredient setmelanotide. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 27 May 2022.

Setmelanotide for the treatment of obesity and control of hunger associated with POMC, PCSK1 or LEPR deficiency 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.

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

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 September 2022 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (G22-21) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

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

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

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Setmelanotide (Imcivree) in accordance with the product information

Imcivree is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 6 years of age and above.

Therapeutic indication of the resolution (resolution of 1 December 2022):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

Adults, adolescents and children 6 years and older with POMC, PCSK1 or LEPR deficiency for the treatment of obesity and the control of hunger

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

Justification:

For the benefit assessment, the pharmaceutical company submits data from the two open-label, multicentre, single-arm, non-randomised phase III 012 and 015 studies. The two studies investigate the efficacy and safety of setmelanotide in patients with POMC-/PCSK1-deficiency obesity (012 study) and with LEPR-deficiency obesity (015 study). A dose titration phase of up to 12 weeks was followed by a 10-week treatment phase with setmelanotide. All patients who had lost at least 5 kg (or 5% if baseline < 100 kg) of weight from baseline after the open-label treatment phase and who continued to tolerate setmelanotide well were allowed to participate in the rest of the study. All other patients were excluded from active treatment.

The 10-week treatment phase with setmelanotide was followed by a so-called withdrawal phase, in which setmelanotide was discontinued and the patients received placebo for 4 weeks and subsequently setmelanotide again (blinded). This was followed by a 32-week treatment phase with setmelanotide.

The studies were open to patients aged 6 years and older with genetically confirmed POMC or PCSK1-deficiency obesity (012 study) or LEPR-deficiency obesity (015 study). All patients had to be obese according to the following criteria: Obesity ≥ 95. Percentile for the respective age group (for children and adolescents) or BMI ≥ 30 kg/m^2 (for adults). Relevant exclusion criterion for the studies was a previous bariatric surgery with a permanent weight loss of > 10% compared to pre-surgery; patients with a weight loss < 10% or an unsuccessful surgery, however, were eligible for study participation. The study duration was approximately 52 weeks and the primary efficacy endpoint in the studies was the percentage of patients with a pre-specified weight reduction ≥ 10% after 1 year of treatment.

Patients with a good response to setmelanotide who successfully completed the 012 or 015 study had the option of continuing treatment in the follow-up RM-493-022 study. This study has not yet been finalised.

A total of 15 patients were enrolled in each of the two studies. The patients were between 7 and 37 years old (median 16 years in the 012 study and 23 years in the 015 study). The majority of the patients were at least 12 years old (approx. 67% in the 012 study and approx. 93% in 015 study). The patients weighed a median of 114 kg (median BMI 39 kg/m^2) at baseline in the 012 study and 132 kg (median BMI 47 kg/m^2) in the 015 study.
All patients in the studies received one or more treatments for different concomitant diseases, such as treatments for adrenocorticotropic hormone deficiency, arterial hypertension and diabetes mellitus (012 study) or treatments for vitamin D deficiency/ prophylaxis, hypothyroidism and disorders of physical maturation (015 study).

Mortality

The number of deaths was collected in the 012 and 015 studies as part of the safety assessment. There was one death in the 015 study.

Morbidity

Body weight and Body Mass Index (BMI)

In both studies, body weight and height were recorded in triplicate at each visit. The BMI or the age-adjusted BMI z score (age group < 18 years) was determined on the basis of body weight and height.

The anthropometric parameters of body weight and BMI are important in the present indication because weight gain is a central characteristic of POMC, PCSK1 or LEPR-deficiency obesity. These endpoints are assessed as significant morbidity parameters in the present therapeutic indication. Data adjusted for age and sex (z scores) are preferred over absolute values.

The primary endpoint in both studies was the percentage of patients with ≥ 10% weight reduction at week 52 compared to baseline. In both studies, a relevant proportion of patients achieved a weight reduction of ≥ 10% after 52 weeks (012 study: 12 out of 14 patients, 015 study: 8 out of 15 patients).

The results of the 8-week withdrawal phase are not used separately for the benefit assessment. Although the 012 study showed that the patients regained body weight during the 4-week discontinuation of setmelanotide, it is uncertain to what extent the increase in body weight is comparable to the natural course of the disease and thus, to what extent further findings relevant for the benefit assessment can be derived.

With regard to BMI, the patients in the 012 study showed a relevant reduction in BMI at week 52 compared to baseline. In the 015 study, the percentage of patients in the evaluation was below 70%, based on the patients originally enrolled, which is why the data are not taken into account in the benefit assessment.

As only patient listings are available for the BMI z score for the age group < 18 years, the data cannot be used for the benefit assessment.

In both single-arm studies, a reduction in body weight was observed after 52 weeks compared to baseline, and in the 012 study a reduction in BMI was also observed. However, usable data on age-related BMI (BMI z score) are not available.

While the values at baseline indicate a significantly higher body weight and BMI of the children, adolescents and adults compared to the normal population, at the end of the study after 52 weeks the anthropometric values are not yet in the range of age-matched subjects of the normal population, but the results indicate a significant reduction of body weight and BMI.

With regard to the natural course of the disease, it can be noted that the affected patients continuously gain body weight, thus developing pronounced obesity. This is associated with a greatly increased mortality and morbidity rate[2]. In particular, cardiovascular, metabolic, respiratory and orthopaedic complications are relevant, which can occur as early as childhood. Against this background, in the present therapeutic indication of POMC, PCSK1 and LEPR-deficiency obesity, the relative weight loss and the reduction of BMI are of significant clinical importance, which could not be achieved until now due to the insufficient treatment options. However, with the present genetic diseases, it can be assumed with sufficient certainty that no spontaneous improvements occur in the natural course of the disease.

Overall, the data presented can nevertheless only be interpreted with difficulty in terms of their significance, as no assessment is possible on the basis of the data presented in comparison to the natural course of the disease in the present patient population. In principle, however, a relative weight loss or reduction of the BMI should be considered as a therapeutic goal in this therapeutic indication, as these represent the relevant manifestation of the present genetically based obesity and are causal for the associated comorbidities. Nevertheless, it would have been desirable to collect additional morbidity endpoints that could show the effects of obesity on the patients (e.g., pain, physical resilience, restriction in everyday activities).

Taken together, the administration of setmelanotide showed a relevant reduction in body weight and BMI at week 52 compared to baseline, but the extent of these reductions is non-quantifiable.

Hunger

The endpoint "hunger" was assessed in the studies using the questionnaire "Hunger Score". The survey was conducted using the "Daily Hunger Questionnaire" and the "Global Hunger Questionnaire".

The Daily Hunger Questionnaire assessed daily hunger before breakfast. For patients ≥ 12 years of age, an 11-point Likert scale was used to map hunger from 0 (= not hungry) to 10 (= greatest possible hunger). For children in the age group 6 to < 12 years, a 5-point Likert scale with a smiley system was used. The endpoint was collected via the operationalisation "improvement of the hunger by 25%" in the studies, whereby the relevance of the threshold value was not sufficiently justified.

The Global Hunger Questionnaire included the Patient Global Impression of Severity (PGIS), which included global hunger status with 4 response options (none, mild, moderate and severe), and the Patient Global Impression of Change (PGIC) on change in hunger status with 5 response options (significantly less hungry, slightly less hungry, no change, slightly hungrier, significantly hungrier) each at week 52 compared to baseline.

Overall, it is questionable to what extent the included study population, especially children, in the present clinical picture with strong hunger or the presence of hyperphagia, can quantify

[2] see also Assessment Report of the European Medicines Agency (EMA) on setmelanotide (Imcivree), https://www.ema.europa.eu/en/documents/assessment-report/imcivree-epar-public-assessment-report_en.pdf (last accessed: 3. November 2022).

an assessment with regard to the present as well as the initial status of hunger and make a mental subtraction from this. Instead, it is assumed that this estimate largely captures the current hunger. This effect becomes greater the longer the recall interval is.

In principle, the endpoint "hunger" is attributed great importance in the present indication, since the extreme hunger of the patients is, on the one hand, causal for the weight gain, thus also representing a central characteristic of POMC, PCSK1 or LEPR-deficiency obesity. On the other, the lack of control over hunger is accompanied by great suffering for the patients. However, it is generally assumed that hunger is a very subjective feeling with strong relevance at the individual level. It remains unclear to what extent hunger leads to an impairment, such as in the perception of everyday activities or the quality of life. In addition, there are the already described uncertainties regarding the assessment of hunger over a certain period of time.

Particularly against the background of these uncertainties, the "Global Hunger Questionnaire" is not taken into account for the benefit assessment, as this surveyed the global hunger status over a very long recall interval (week 52 compared to baseline). Despite the uncertainties, the "Daily Hunger Questionnaire" is presented additionally for the benefit assessment.

With regard to the Daily Hunger Questionnaire, more than half of the patients ≥ 12 years of age showed an improvement of ≥ 25% in their hunger in both studies.

The results of the 8-week withdrawal phase are not used separately for the benefit assessment.

Quality of life

With regard to health-related quality of life, the (patient-reported) questionnaires Impact of Weight on Quality of Life (IWQOL)-Lite, Paediatric Quality of Life (PedsQL) and Short Form 36 (SF-36) were recorded in the two studies. However, due to the low return rates at baseline and during the course of the study, or due to a lack of evaluations at the aggregate level, the data presented cannot be taken into account in the benefit assessment.

Side effects

Adverse events (AEs) and serious adverse events (SAEs) were recorded in the 012 and 015 studies in the period between setmelanotide administration and 30 days after setmelanotide administration.

In the 012 study, none of the patients had an AE of severity grade ≥ 3 and about 40% of the patients had an SAE. In the 015 study, AE of severity grade ≥ 3 occurred in approx. 20% and SAE in approx. 20% of patients. Only one patient dropped out of the 015 study due to an AE.

Depressiveness and suicidality

Subjects with severe obesity show more depressive symptomatology and suicidality. In addition, the EMA[2] points out that medicinal products that are active in the central nervous system may be associated with depressiveness and suicidality. Both depressiveness and suicidality were assessed in the 012 and 015 studies as part of the AEs.

Depressiveness was assessed in the 012 and 015 studies using the Patient Health Questionnaire 9 (PHQ-9), a screening instrument for diagnosing depressiveness. The questionnaire assesses the severity of depressive symptomatology in the age group ≥ 12 years by means of a self-assessment over the last 2 weeks. The sum score scale of the PHQ-9 can be

divided into 4 categories to map the severity of depressive symptomatology: 0 to 4 = minimal; 5 to 9 = mild; 10 to 14 = moderate; 15 to 27 = severe.

In the 012 study, there were no statistically significant differences in depressive symptomatology at 52 weeks compared to baseline following the administration of setmelanotide. However, due to the low return rates in the course of the 015 study, the data presented cannot be considered in the benefit assessment.

Suicidality was assessed in the 012 and 015 studies using the Columbia Suicide Severity Rating Scale (C-SSRS). However, due to the low return rates at baseline and during the course of the study, the data presented cannot be taken into account in the benefit assessment.

Overall assessment

For setmelanotide for the treatment of POMC, PCSK1 or LEPR deficiency obesity and the control of hunger in adults, adolescents and children 6 years and older, results on mortality, morbidity, quality of life and side effects are available from the single-arm 012 and 015 studies.

One death was recorded in the 015 study.

In the endpoint category of morbidity, a relevant reduction in body weight was observed in both single-arm studies after 52 weeks and a relevant reduction in BMI was observed in the 012 study, both compared to baseline. However, usable data on age-related BMI (BMI z score) are not available. Due to the natural course of POMC, PCSK1 or LEPR-deficiency obesity, which is associated with a continuously increasing body weight gain of the affected patients and with the development of pronounced obesity and is causal for the associated comorbidities, the relative weight loss or the reduction of BMI is of significant clinical importance in the present therapeutic indication.

The data on health-related quality of life cannot be used for the benefit assessment because the return rates are too low.

With regard to the results on side effects, severe (grade ≥ 3) and serious adverse events (SAEs) as well as therapy discontinuation due to AEs occurred in part during treatment with setmelanotide. In the 012 study, there were no statistically significant differences in depressiveness after 52 weeks compared to baseline; the results of the 015 study and suicidality in both studies cannot be used for the benefit assessment due to the very low return rates.

Overall, the administration of setmelanotide resulted in a relevant reduction in body weight and BMI at week 52 compared to baseline, although the extent of these reductions is non-quantifiable. Against this background, a non-quantifiable additional benefit is identified for setmelanotide for the treatment of POMC, PCSK1 or LEPR deficiency obesity and the control of hunger in adults, adolescents and children aged 6 years and older because the scientific data basis does not allow quantification.

Significance of the evidence

There is a high risk of bias at study level for the 012 and 015 studies presented due to the single-arm, open-label study design.

In addition, only patients who achieved a minimum weight loss during setmelanotide administration and showed good tolerability of setmelanotide were allowed to be treated in the further course of the studies. Consequently, only patients with a good response to setmelanotide over 40 weeks will be continued in the study. Against this background, there

are uncertainties as to whether the study population represents the entire therapeutic indication of setmelanotide.

Against this background, the reliability of data is classified under the "hint" category.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Imcivree" with the active ingredient setmelanotide. Imcivree was approved as an orphan drug. The therapeutic indication assessed here is as follows: "Treatment of POMC, PCSK1 or LEPR deficiency obesity and control of hunger in adults, adolescents and children 6 years and older".

The pharmaceutical company submits data on mortality, morbidity, quality of life and side effects of the single-arm 012 and 015 studies for the benefit assessment.

One death was recorded in the 015 study.

In the endpoint category of morbidity, a relevant reduction in body weight and BMI (in the 012 study) was observed in both single-arm studies after 52 weeks, each compared to baseline. However, usable data on age-related BMI are not available. Due to the natural course of POMC, PCSK1 or LEPR-deficiency obesity, which is associated with a continuously increasing body weight gain of the affected patients and with the development of pronounced obesity and is causal for the associated comorbidities, the relative weight loss or the reduction of BMI is of significant clinical importance in the present therapeutic indication.

Usable data on health-related quality of life are not available.

With regard to the results on side effects, severe (grade ≥ 3) and serious adverse events (SAEs) as well as therapy discontinuation due to AEs occurred in part during treatment with setmelanotide. In the 012 study, there were no statistically significant differences in depressiveness compared to baseline after 52 weeks. Usable data for depressiveness in the 015 study and for suicidality in both studies are not available.

Due to the single-arm, open-label design of the 012 and 015 studies, there is a high risk of bias at the study level. In addition, there are uncertainties as to whether the study population represents the entire therapeutic indication of setmelanotide, as only patients who showed a minimum weight loss and good tolerability of setmelanotide were treated in the further course of the study.

Overall, the administration of setmelanotide resulted in a relevant reduction in body weight and BMI at week 52 compared to baseline, although the extent of these reductions is non-quantifiable. Against this background, a hint for a non-quantifiable additional benefit is identified for setmelanotide for the treatment of POMC, PCSK1 or LEPR deficiency obesity and the control of hunger in adults, adolescents and children aged 6 years and older because the scientific data basis does not allow quantification.

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

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

The stated range of approx. 140 to 280 patients is subject to uncertainties. In particular, there are uncertainties regarding the prevalence of LEPR deficiency obesity estimated by the

pharmaceutical company. Overall, the range is therefore considered to be overestimated in all likelihood.

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 Imcivree (active ingredient: setmelanotide) at the following publicly accessible link (last access: 7 November 2022):

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

Treatment with setmelanotide should only be initiated and monitored by doctors experienced in treating obesity with underlying genetic aetiology.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 November 2022).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g., because of side effects or co-morbidities) 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.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The information on treatment duration and dosage was taken from the corresponding product information.

The initial daily dose of setmelanotide in children 6 to 11 years of age is 0.5 mg, and can be increased to 2 mg from week 6. According to the product information, the dose for patients of this age can be further increased to 2.5 mg. Patients 12 years and older start with a daily initial dose of 1 mg which can be increased to 2 mg daily from week 3. The daily dose can be increased to a maximum of 3 mg according to the product information.

The appropriate dose of setmelanotide is injected subcutaneously daily.

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				
Setmelanotide	continuously, 1 x daily	365	1	365

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Children aged 6 to 11 years					
Setmelanotide	0.5 mg - 2.5 mg	0.5 mg - 2.5 mg	1 x 0.5 mg - 1 x 2.5 mg	365	365 x 0.5 mg - 365 x 2.5 mg
Adolescents and adults 12 years of age and above					
Setmelanotide	1 mg - 3 mg	1 mg - 3 mg	1 x 1 mg - 1 x 3 mg	365	365 x 1 mg - 365 x 3 mg

Costs:

Costs of the medicinal products:

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.

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					
Setmelanotide 10 mg/ml	3 - 20 SD	€ 3,381.10	€ 1.77	€ 192.50	€ 3,186.83
Abbreviations: SD = single doses					

LAUER-TAXE® last revised: 15 November 2022

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.

No additionally required SHI services are taken into account for the cost representation.

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

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

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

3. Bureaucratic costs calculation

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

4. Process sequence

On 27 May 2022, the pharmaceutical company submitted a dossier for the benefit assessment of setmelanotide to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 September 2022 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 September 2022.

The oral hearing was held on 10 October 2022.

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 22 November 2022, and the proposed resolution was approved.

At its session on 1 December 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 August 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	5 October 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	10 October 2022	Conduct of the oral hearing
Working group Section 35a	19 October 2022 2 November 2022 16 November 2022	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	22 November 2022	Concluding discussion of the draft resolution
Plenum	1 December 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 1 December 2022

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

Prof. Hecken