Gemeinsamer Bundesausschuss

Justification

to 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 (new therapeutic indication: obesity and control of hunger, POMC, PCSK1, LEPR deficiency or Bardet-Biedl syndrome, ≥ 2 to < 6 years)

of 21 August 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all 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 SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

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

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation the G-BA modified the procedure for the benefit assessment of orphan drugs at their 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 their 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 is 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 17 October 2024, there is an exemption - irrespective of age - from the prescription exclusion for setmelanotide in relation to genetically confirmed Bardet-Biedl syndrome, loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency (effective date 13 January 2025).

The active ingredient setmelanotide (Imcivree) was listed for the first time on 1 June 2022 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices. On 26 July 2024, setmelanotide 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, 12.12.2008, sentence 7).

At the request of the Federal Joint Committee (G-BA), the pharmaceutical company submitted a dossier on the active ingredient setmelanotide with the new therapeutic indication "For the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS), loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in children 2 to < 6 years of age" in due time on 19 February 2025.

Setmelanotide for the treatment of obesity and control of hunger associated with POMC, PCSK1, LEPR deficiency or BBS 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 assess 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 2 June 2025 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 have adopted their 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 (IQWiG G25-10) 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 have evaluated the studies relevant for the marketing authorisation with regard to 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.

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

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 Bardet-Biedl syndrome (BBS), loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in adults and children 2 years of age and above.

Therapeutic indication of the resolution (resolution of 21 August 2025):

IMCIVREE is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS), loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency in children 2 to < 6 years of age.

2.1.2 Extent of the additional benefit and significance of the evidence

Children 2 to < 6 years of age with genetically confirmed Bardet-Biedl syndrome, 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:

The pharmaceutical company presented the single-arm, open-label, multicentre approval study RM-493-033 for the benefit assessment. The study investigates the safety and efficacy of setmelanotide in the treatment of obesity associated with genetically confirmed Bardet-

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

Biedl syndrome (BBS), POMC/PCKS1 deficiency or LEPR deficiency in children 2 to < 6 years of age.

A dose titration phase of 2 to 6 weeks is followed by an open-label treatment phase. In total, the study duration (including dose titration) covers a period of 52 weeks. The study was conducted in 6 study sites in Australia, the UK, Spain and the USA.

Body mass index (BMI) was the primary endpoint of the study.

A total of 12 subjects were enrolled in the study, including 7 subjects with POMC, PCSK1 or LEPR deficiency (PPL) and 5 subjects with BBS. The end of the study was the time of the final data cut-off on 18 September 2023 (pre-specified data cut-off). At this point in time, 11 subjects had completed the 52-week treatment phase and one subject had discontinued the study prematurely (last visit at week 8). Subsequently, 8 of the 11 subjects received setmelanotide during transitional visits until the initiation of long-term extension (long-term therapy). The other 3 subjects had already crossed the age limit of 6 years and over for the previously existing marketing authorisation, and received setmelanotide commercially outside the study.

The median age (min; max) of the enrolled participants was 3.5 years (2; 5). The inclusion criterion was a minimum weight of 15 kg. The median (min; max) weight at baseline was 38.5 kg (17.8; 69.6). In terms of genotype, 5 subjects had a mutation in one of the BBS genes, 3 subjects in the POMC gene and 4 subjects in genes coding for the leptin receptor. No subject with a defect in the PCSK1 gene was enrolled. Obesity was an inclusion criterion and defined as a BMI ≥ 97. Percentiles, corrected for age and sex. Obesity in the medical history was only documented in one subject in the BBS group (20%) and in 4 subjects (57%) in the PPL group. The median BMI of the children at the time of enrolment in the study was 28.7 (19.3; 42.5). The BMI was higher in the PPL group than in the BBS group.

All patients received at least one concomitant medication in the course of the study. The extent to which glucocorticoids (in approx. 42%) were used in a duration and dosage that may have favoured weight gain as a side effect cannot be assessed on the basis of the data.

The dosages used in the study do not correspond to the recommended setmelanotide dosage according to the product information (PI). The possible maximum dose of 2.5 mg (in case of inadequate response and good tolerability) according to PI at a body weight ≥ 40 kg was not offered and used in the study. However, children with a baseline weight of over 40 kg were also enrolled in the study. These study participants may therefore have been under-treated with the intervention under investigation.

Mortality

The number of deaths were collected as part of the safety assessment. No deaths were reported during the 52-week observation period.

Morbidity

Body Mass Index (BMI)

Body weight (kg) was measured at the study site in the mornings, preferably always at the same time. 3 measurements should be taken at each study visit and the average of the measurements taken per study visit should be calculated.

The BMI-z was determined using the WHO Child Growth Standard 2007 as a reference measure.

The anthropometric parameters of body weight and BMI are important in the present indication because weight gain is a core characteristic. 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 mean absolute and percentage change in BMI z-score at study week 52 compared to baseline is used for the benefit assessment. In contrast, the pre-specified evaluation of the percentage of subjects with a reduction in BMI z-score by ≥ 0.2 at week 52 compared to baseline is not used. The relevance of the response criterion of 0.2 could also not be demonstrated on the basis of the literature presented after the oral hearing.

At the start of the study, the median BMI-z in the total study population was approx. 7 standard deviations above the population average of the WHO Child Growth Standard 2007 reference population. Over 52 weeks, there was a change in the median BMI-z by -3 standard deviations. This corresponds to a percentage change of 40.2% at week 52 compared to baseline. The percentage change in the PPL population (52.3%) is more pronounced than in the BBS population (32.9%). However, the PPL population already had a higher median BMI z-score at baseline (9.3) than the BBS population (4.4).

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. In particular, cardiovascular, metabolic, respiratory and orthopaedic complications are relevant, which can occur as early as childhood. Against this background, relative weight loss or BMI reduction is of prime clinical importance in the present therapeutic indication. In the case of 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 these data in comparison to the natural course of the disease in the present patient population. In principle, however, a relative weight loss or reduction in 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 presently shows a relevant reduction in the BMI z-score at week 52 compared to baseline, but the extent of which is non-quantifiable.

Hunger

The data collection on the endpoint of hunger and hunger-related behaviour was carried out using the questionnaire "The Caregiver Reported Global Hunger Questions". The primary objective was to determine the extent and change in hunger. The questions were answered in each case by the caregiver. The reference period is the last 7 days.

The pharmaceutical company presented results for both the Caregiver Global Impression of Severity (CGIS) and the Caregiver Global Impression of Change (CGIC). The CGIS comprises 4 response options for the severity of global hunger status (not at all hungry, slightly hungry, moderately hungry, very hungry); the CGIC comprises 5 response options for the change in global hunger status (much less hungry, somewhat less hungry, no change in hunger behaviour, somewhat hungrier, much hungrier).

In principle, the endpoint "hunger" is attributed great significance in the present indication, since the extreme hunger of the patients is, on the one hand, responsible for the weight gain and represents a core characteristic of genetically determined 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 principle, self-assessment is also preferred for the benefit assessment. However, self-assessment by all patients appears to be hardly implementable in the patient population of 2 to < 6-year-olds considered here, which is why the collection of the endpoint by another subject is considered justifiable. As the caregivers are primarily the parents of the test subjects, a close patient-caregiver relationship is assumed.

Despite these uncertainties, the results of the CGIS are therefore presented additionally for the benefit assessment.

At the start of the study, 75% of the study participants were moderately hungry (5 subjects 41.7%) to very hungry (4 subjects 33.3%). The remaining 25% (3 subjects) were "not hungry at all". At week 52, all 4 subjects who were very hungry had improved by at least one category. 3 of the "moderately hungry" subjects also improved by one category. However, all 3 subjects who were "not hungry at all" at baseline also deteriorated by at least one category.

In the retrospective assessment of hunger, as was done for the CGIC, caregivers must be able to quantify both the current status and the baseline status, and perform a mental subtraction from this. It is conceivable that this estimate largely captures the current hunger. This effect becomes greater the longer the recall interval is. In addition, diseases with high symptom variability are particularly prone to this form of risk of bias (recall bias).

Particularly against the background of these uncertainties, the CGIC 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).

Quality of life

The pharmaceutical company submitted data on the "PROMIS Global health parent proxy questionnaire" and the "PROMIS Global health questionnaire".

The results of the "PROMIS Global health parent proxy questionnaire" are not used for the benefit assessment due to insufficient validation in the population of the therapeutic indication. The PROMIS parent proxy instruments have been developed and validated for the parent-reported assessment of the quality of life of children 5 to 17 years of age. However, a clear majority of the children enrolled in the RM-493-033 study (at least n = 10 of N = 12) were under 5 years old. No validation studies in children < 5 years of age could be identified even in indicative literature researches. Accordingly, the PROMIS Global health parent proxy questionnaire cannot be considered validated in the present study population.

The "PROMIS Global health questionnaire" was used to survey the quality of life of parents/ caregivers, which is not relevant for the benefit assessment.

As a result, no suitable data on the endpoint category of health-related quality of life are thus available for the present benefit assessment.

Side effects

The median treatment duration was 52.2 weeks. According to the study documents, safety was monitored until 30 days after the last administration of the study medication.

No serious or severe adverse events were observed in the RM-493-033 study. Therapy discontinuation due to adverse events also did not occur.

Overall assessment

The pharmaceutical company presented the single-arm, open-label, multicentre approval study RM-493-033 for the benefit assessment. The study covers a period of 52 weeks. A total of 12 subjects were examined in the study (7 subjects with PPL and 5 subjects with BBS).

No deaths were reported during the 52-week observation period.

For the endpoint category of morbidity, the administration of setmelanotide at week 52 showed a relevant reduction in the BMI z-score compared to baseline. Due to the natural course of the genetically determined disease, which is associated with a continuously increasing body weight of the affected patients and with the development of pronounced obesity and is the root cause of the associated comorbidities, the reduction in BMI is of prime clinical importance in the present therapeutic indication.

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

No serious or severe adverse events were observed for the endpoint category of side effects. Therapy discontinuation due to adverse events also did not occur.

In the overall assessment, the administration of setmelanotide at week 52 showed a relevant reduction in the BMI z-score compared to baseline. However, the extent of the benefit is non-quantifiable as the single-arm data presented does not allow a comparison with the natural course of the disease. Against this background, a non-quantifiable additional benefit of setmelanotide is identified for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome, POMC, PCSK1 or LEPR deficiency in children aged 2 to < 6 years, since the scientific data does not allow quantification.

Significance of the evidence

The present benefit assessment is based on the single-arm approval study RM-493-033. This study therefore did not compare setmelanotide with a control group. Due to the lack of a comparator group, the risk of bias of the study at study and endpoint level is assessed as high.

Furthermore, the significance of the data presented is limited due to the small number of patients examined (12 subjects).

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

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient setmelanotide.

IMCIVREE was approved as an orphan drug. The therapeutic indication assessed here is as follows: IMCIVREE is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS), loss-of-function biallelic pro-opiomelanocortin (POMC), including PCSK1, deficiency or biallelic leptin receptor (LEPR) deficiency (PPL) in children 2 to < 6 years of age.

Children 2 to < 6 years of age with genetically confirmed Bardet-Biedl syndrome, POMC, PCSK1 or LEPR deficiency for the treatment of obesity and the control of hunger

For this patient group, the pharmaceutical company presented the single-arm, open-label, multicentre approval study RM-493-033. The study covers a period of 52 weeks. A total of 12 subjects were examined in the study (7 subjects with PPL and 5 subjects with BBS).

No deaths were reported.

For the morbidity endpoint category, the administration of setmelanotide at week 52 showed a relevant reduction in the BMI-z score compared to baseline, which is of prime clinical importance in the present therapeutic indication due to the genetically determined continuous weight gain.

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

No serious or severe adverse events were observed for the endpoint category of side effects. Therapy discontinuation due to adverse events also did not occur.

In the overall assessment, the administration of setmelanotide at week 52 showed a relevant reduction in the BMI z-score compared to baseline. However, the extent of the benefit is non-quantifiable as the single-arm data presented does not allow a comparison with the natural course of the disease. Against this background, a non-quantifiable additional benefit of setmelanotide is identified for the treatment of obesity and the control of hunger associated with BBS or PPL in children aged 2 to < 6 years, since the scientific data does not allow quantification.

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

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

The resolution is based on the information on the number of children with BBS from the dossier assessment of the IQWiG (mandate G25-10). The number of children with POMC deficiency (including PCSK1) or LEPR deficiency is based on the information from the benefit assessment dossier of the pharmaceutical company.

Children with BBS:

The information provided by the pharmaceutical company is subject to uncertainty, which is in particular due to the older evidence and the question of the transferability of the percentages used to the age group relevant here.

Based on the information provided by the pharmaceutical company, it is possible that the prevalence data for the lower limit is potentially underestimated, as various genotypes of BBS may not have been known at the time of the respective examinations. Furthermore, the criteria of obesity or the control of hunger mentioned in the therapeutic indication are operationalised via the sole presence of obesity. It therefore remains unclear whether the therapeutic indication also applies to non-obese subjects with BBS and hunger to be controlled. Against this background, IQWiG recommends using the range of 72% to 92% for the percentage of obese subjects with BBS instead of the mean value. Taking this range for the percentage of obese children into account results in a SHI target population of approx. 18 to 56 subjects.

Children with POMC deficiency (including PCSK1) or LEPR deficiency:

The pharmaceutical company states a number of approx. 6 – 11 subjects for the SHI target population of children with POMC deficiency (including PCSK1) or LEPR deficiency. The determined prevalence data are subject to uncertainty, as the relevant obesity associated with LEPR deficiency is listed under a different ORPHAcode (179494 "Obesity due to leptin receptor gene mutations") than the one used by the pharmaceutical company (ORPHAcode 66628).

As a result, the SHI target population is the sum of the number of children with BBS (18 – 56 children) and the number of children with POMC deficiency (including PCSK1) or LEPR deficiency (6 – 11 children).

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: 4 April 2025):

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 specialists experienced in treating patients with 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: 1 June 2025).

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 varies from patient to patient 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 product information recommends a dose of 0.5 mg setmelanotide once a day for paediatric patients 2 to 5 years of age with a body weight below 20 kg. For children with a body weight 20 kg or more, the dose should be titrated. The daily starting dose of setmelanotide at a body weight between 20 and 30 kg is 0.5 mg, and can be increased to 1 mg from week 3.

The appropriate dose of setmelanotide is injected subcutaneously daily.

Treatment period:

Children 2 to < 6 years of age with genetically confirmed Bardet-Biedl syndrome, POMC, PCSK1 or LEPR deficiency for the treatment of obesity and the control of hunger

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	365.0	1	365.0

Consumption:

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.

The average body measurements were applied for dosages depending on body weight (BW) or body surface area (BSA) (average height of a 2-year-old child: 14.1 kg, average body weight of a 5-year-old child: 20.8 kg).[2]

Children 2 to < 6 years of age with genetically confirmed Bardet-Biedl syndrome, POMC, PCSK1 or LEPR deficiency for the treatment of obesity and the control of hunger

[2] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

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 2 to 5 years, body weight < 20 kg					
Setmelanotide	0.5 mg	0.5 mg	1 x 0.5 mg	365.0	365 x 0.5 mg
Children aged 2 to 5 years, body weight ≥ 20 kg					
Setmelanotide	0.5 mg - 1 mg	0.5 mg - 1 mg	1 x 0.5 mg - 1 x 1 mg	365.0	365 x 0.5 mg - 365 x 1 mg

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 reference prices shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

Children 2 to < 6 years of age with genetically confirmed Bardet-Biedl syndrome, POMC, PCSK1 or LEPR deficiency for the treatment of obesity and the control of hunger

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	10 SFI each 10 mg	€ 20,048.17	€ 1.77	€ 1,144.36	€ 18,902.04
Abbreviations: SFI = solution for injection (vials)					

LAUER-TAXE® last revised: 1 August 2025

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 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 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.

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 have 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 have 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 requirements 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 have 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:

Children 2 to < 6 years of age with genetically confirmed Bardet-Biedl syndrome, POMC, PCSK1 or LEPR deficiency for the treatment of obesity and the control of hunger

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.

References:
Product information for setmelanotide (Imcivree); Imcivree 10 mg/ml solution for injection; last revised: 26 July 2024

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 19 February 2025 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 2 VerfO.

The benefit assessment of the G-BA was published on 2 June 2025 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 statements was 23 June 2025.

The oral hearing was held on 7 July 2025.

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 12 August 2025, and the draft resolution was approved.

At their session on 21 August 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	27 May 2025	Information of the benefit assessment of the G-BA
Working group Section 35a	1 July 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	7 July 2025	Conduct of the oral hearing
Working group Section 35a	15 July 2025 5 August 2025	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	12 August 2025	Concluding discussion of the draft resolution
Plenum	21 August 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 21 August 2025

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

Prof. Hecken