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 (new therapeutic indication: obesity and control of hunger, Bardet-Biedl syndrome, ≥ 6 years)

of 2 November 2023

Contents

1. Legal basis

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

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

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

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

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section

35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published 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 16 February 2023, setmelanotide is exempt from exclusion from prescription in connection with genetically confirmed Bardet-Biedl syndrome in adults and children 6 years of age and above (entry into force on 20 April 2023).

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 2 September 2022, 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 for the active ingredient setmelanotide with the new therapeutic indication "Obesity and control of hunger associated with genetically confirmed Bardet-Biedl syndrome in adults and children 6 years of age and above" by the deadline of 15 May 2023.

Setmelanotide for the treatment of obesity and control of hunger associated with Bardet-Biedl syndrome 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 July 2021.

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

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 August 2023 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 pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and

patient numbers (IQWiG G23-12) and the statements made in the written statement and oral hearing procedure, as well as the amendment to the benefit assessment drawn up by the G-BA.

In order to determine the extent of the additional benefit, the G-BA has 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.

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 6 years of age and above.

Therapeutic indication of the resolution (resolution of 2 November 2023):

Imcivree is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed Bardet-Biedl syndrome (BBS) in adults and children 6 years of age and above.

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 of age and above with genetically confirmed Bardet-Biedl syndrome (BBS) 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 assessment of the additional benefit, the pharmaceutical company submits the results of the label-enabling study RM-493-023.

The RM-493-023 study is a multicentre phase III study with a 14-week randomised placebo-controlled treatment phase, followed by an open treatment phase of 52 weeks, into which subjects who were randomised to the placebo arm in the controlled phase were also transferred. Subjects 6 years of age and older with BBS or with Alström syndrome obesity were enrolled. Patients with Alström syndrome are not covered by the marketing authorisation. Only the study population with BBS is relevant for the benefit assessment.

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

A total of 44 subjects with BBS who were assigned in a 1:1 ratio to treatment with setmelanotide (N = 22) or to the placebo group (N = 22) were enrolled in the study. During the study, setmelanotide was used in a dosage that was in line with the product information. 32 of the 44 study participants in total were enrolled in the pivotal cohort and 12 subjects in the supplemental cohort. The pivotal cohort was pre-specified to conduct the primary analysis, for which results were submitted as part of the marketing authorisation. The supplementary cohort was used to obtain additional evidence after recruitment of the pivotal cohort had been completed.

The primary endpoint of the study was a weight reduction of ≥ 10% at study week 52. Other endpoints included the change in body weight, the change in body mass index (BMI) and the age-adjusted BMI z-score, quality of life and side effects. At the end of the placebo-controlled treatment phase, only selected endpoints were collected. Analyses of changes in body weight, BMI, BMI z-score and safety are available for study week 14.

Patient-reported endpoints were measured using different instruments depending on the presence of cognitive impairment. However, the definition of subjects with cognitive impairment remains unclear.

Analyses were planned in the placebo-controlled phase at study week 14 and in the single-arm phase at treatment week 52. Documents subsequently submitted as part of the written statement procedure show, among other things, that the treatment or duration of observation relevant for the analysis of the single-arm 52-week study phase was not reached in a total of 11 of the 32 study participants in the pivotal cohort. For 8 of these subjects, the shortfall was at least 2 weeks for at least one of the planned time values. With regard to the collection of side effects, the duration of observation of the total population of subjects with BBS cannot be identified in the submitted study documents. The median treatment duration was 53 weeks.

BBS shows a clinically and genetically heterogeneous clinical picture. In addition to obesity, there are other disease manifestations that modify body weight. The multigenetic disease leads to a variety of other symptoms such as renal failure, diabetes mellitus, depression or mental impairment, all of which could affect body weight.

The results of the single-arm study phase are therefore subject to considerable uncertainty with regard to the study design and the evaluations performed. In particular, there are uncertainties with regard to the single-arm design and with regard to imputation procedures for replacing missing values.

Furthermore, study results are not available for all age groups covered by the therapeutic indication. For example, the results presented on body weight relate exclusively to subjects 12 years of age and above (n = 36). In contrast, results on efficacy endpoints for children between 6 and 12 years of age (n = 8) are only available to a limited extent. Furthermore, no results are available for subjects with BBS who are older than 46 years.

For the present benefit assessment, the comparator data of the placebo-controlled study phase at study week 14 are considered. The data from the single-arm study phase will not be used to quantify the additional benefit.

Mortality

The number of deaths in the RM-493-023 study was recorded continuously over the entire duration of the study as part of the safety assessment. There were no deaths in the total study population.

Morbidity

Body weight and Body Mass Index (BMI)

During both the placebo-controlled and the single-arm treatment phases, body weight and body height were each measured three times at each visit as part of standardised measurements.

The anthropometric parameters of body weight and BMI are important in the present indication because weight gain is an early-onset central characteristic of BBS. 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.

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).

At the end of the controlled study phase at week 14, statistically significant reductions in body weight, BMI and BMI z-score were shown with setmelanotide compared to placebo.

In general, however, the clinical relevance of the observed reduction in body weight remains questionable in view of the high initial weight at the start of the study.

Hunger

The endpoint "hunger" was assessed daily, depending on the presence of cognitive impairment, using the "Daily Hunger Questionnaires" by means of self-reporting and the "Prader-Willi Syndrome Food Problem Diary" by means of external data collection by carers.

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 BBS. 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. This limits the significance of the available questionnaires. In addition, it remains unclear to what extent hunger leads to an impairment, such as in the perception of everyday activities or the quality of life.

Only the results of the "Daily Hunger Questionnaire" are available for the placebo-controlled study phase. Due to the low return rate (< 70%) of all patient-reported endpoints and uncertainties regarding the statistical methods used, the data presented cannot be considered in the benefit assessment.

Hip girth and lipid profile

The endpoints "hip girth" and "lipid profile" are not considered in the benefit assessment due to the lack of patient relevance. Proof of suitability as surrogate endpoints for patient-relevant endpoints was not provided.

General health status (EQ-5D-5L)

The EQ-5D-5L is a questionnaire for collecting health status and is generally used to derive preference-based utility values in the context of health economic assessments.

Only the general health status assessed using the EQ-5D-5L visual analogue scale (VAS) can be considered as a patient-relevant morbidity endpoint in the benefit assessment. With the VAS, the study participants rate their general health status on a scale from 0 to 100 in relation to the current day. A value of 0 corresponds to the worst perceivable health status and a value of 100 to the best perceivable health status.

Results for this endpoint were only presented at study week 52.

Reduction in body weight by at least 10% at week 52

The primary endpoint of the RM-493-023 study, *number of subjects with a weight reduction ≥ 10% in subjects older than 12 years,* was only collected at the end of the single-arm study phase. The endpoint is not considered for the quantification of the additional benefit of setmelanotide due to the uncertainties regarding the study design and evaluation methodology of the single-arm study phase.

Quality of life

Health-related quality of life was assessed in subjects with BBS using the (patient-reported) Impact of Weight on Quality of Life (IWQOL)-Lite and Paediatric Quality of Life (PedsQL) questionnaires.

No results on quality of life were reported for the placebo-controlled treatment phase.

Side effects

Adverse events (AEs) and serious adverse events (SAEs) were collected continuously during the course of the study.

As there are no additional evaluations that do not take disease-related events into account, it cannot be ruled out that events related to the underlying disease were included in the collection of AEs-.

In the side effects category, three serious AEs and no AEs with a CTCAE severity grade ≥ 3 occurred up to week 14.

No effect estimators were submitted. It is therefore not possible to conclusively analyse the side effects in this case.

Overall assessment

For setmelanotide for the treatment of obesity and the control of hunger in adults, adolescents and children 6 years of age and older with genetically confirmed BBS, results on mortality, morbidity, quality of life and side effects are available from the 14-week randomised, placebo-controlled treatment phase of the RM-493-023 study.

In the mortality endpoint category, no deaths occurred during the 14-week placebo-controlled study phase. No statements on the extent of additional benefit can be derived for the mortality category.

In the morbidity category, there were statistically significant reductions in body weight, BMI and BMI-z-scores with setmelanotide compared to placebo at the end of the randomised study phase at week 14.

No results were available in the health-related quality of life category for the placebo-controlled study phase.

In the side effects category, three serious AEs and no AEs with a CTCAE severity grade ≥ 3 occurred up to week 14. Effect estimators for the side effects were not submitted. It is therefore not possible to conclusively analyse the side effects in this case.

Irrespective of the question of whether the comparative study duration is sufficient for the BBS, the clinical relevance of the reduction in BMI observed with setmelanotide remains unclear. The massively increased BMI at the start of study remains at a raised level even after study week 14.

Against this background, a non-quantifiable additional benefit is identified for setmelanotide for the treatment of obesity and the control of hunger in adults, adolescents and children 6 years of age and above with genetically confirmed BBS because the scientific data basis does not allow quantification.

Significance of the evidence

This assessment is based on the results of the 14-week randomised and placebo-controlled treatment phase of the RM-493-023 study.

The risk of bias of the placebo-controlled treatment phase is estimated to be high at study level. Uncertainties in the randomised treatment phase arise primarily due to the comparative study duration, which is considered to be short for this therapeutic indication.

Furthermore, the small sample size and the questionable choice of evaluation methodology also mean that no valid quantification of the additional benefit of setmelanotide can be made.

Overall, the significance of the evidence is classified as a hint.

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) in adults and children 6 years of age and above.

For this patient group, the pharmaceutical company presents results of the RM-493-023 study. In the 14-week randomised study phase, setmelanotide was compared with placebo. In addition, results of the single-arm study phase up to treatment week 52 will be presented. The single-arm study phase is not considered for the quantification of the extent of additional benefit due to uncertainties regarding the study design and the evaluation methodology.

In the mortality endpoint category, no deaths occurred during the 14-week placebo-controlled study phase. No statements on the extent of the additional benefit can be derived for the mortality category.

In the morbidity category, there were statistically significant reductions in body weight, BMI and BMI-z-scores with setmelanotide compared to placebo at the end of the randomised study phase at week 14.

In the side effects category, three serious AEs and no AEs with a CTCAE severity grade ≥ 3 occurred up to week 14. Effect estimators for the side effects were not submitted. It is therefore not possible to conclusively analyse the side effects in this case.

Irrespective of the question of whether the comparative study duration is sufficient for the BBS, the clinical relevance of the reduction in BMI observed with setmelanotide remains unclear. The massively increased BMI at the start of study remains at a raised level even after study week 14.

The significance of the evidence is categorised as a "hint" as uncertainties exist primarily with regard to the comparative study duration, which is considered short for the present therapeutic indication, a small sample size and the questionable choice of evaluation methodology.

In the overall assessment, a hint for a non-quantifiable additional benefit of setmelanotide is identified.

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 (mandate G23-12).

The pharmaceutical company's estimate of the lower limit of subjects with BBS is based on 3 publications, some of which refer to studies that are over 50 years old. Since various genotypes of BBS were presumably not yet known at that time, the lower limit given is potentially underestimated. The pharmaceutical company bases its estimates of the upper limit on information from Orphanet. Since no sources are cited for this information, the upper limit of the prevalence range is also subject to uncertainty.

There are also uncertainties regarding the percentage of BBS patients with obesity or uncontrolled hunger. The surveys on which the aforementioned publication is based are also several decades old, which is why transferability to today's target population is questionable. In addition, it is unclear to what extent the information in the publication also includes patients who are not obese but show uncontrolled hunger. For the reasons mentioned, it is calculated using a range for the percentage of obese patients instead of a single value.

Overall, this results in minor deviations from the information provided by the pharmaceutical company with regard to the target population in statutory health insurance.

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: 22 May 2023):

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 requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 October 2023).

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 starting daily dose of setmelanotide in children 6 to 15 years of age is 1 mg, and can be increased to 2 mg from week 2. According to the product information, the dose for patients of this age can be further increased to 3 mg. Patients 16 years and older start with a daily initial dose of 2 mg which can be increased to 3 mg daily from week 3.

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	365.0	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.

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 and adolescents aged 6 to ≤ 15 years					
Setmelanotide	1 mg - 3 mg	1 mg - 3 mg	1 x 1 mg - 3 x 1 mg	365.0	365.0 x 1 mg - 1095.0 x 1 mg
Adolescents and adults 16 years of age and above					
Setmelanotide	2 mg - 3 mg	2 mg - 3 mg	2 x 1 mg - 3 x 1 mg	365.0	730.0 x 1 mg - 1095.0 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 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					
Setmelanotide 10 mg/ml	100 SD each 1 mg	€ 33,717.17	€ 2.00	€ 3,300.00	€ 30,415.17
Abbreviations: SD = single doses					

LAUER-TAXE® last revised: 15 October 2023

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 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.

In the case of information on "determined" or "undetermined" combinations, the assessed medicinal product can be used in a combination therapy according to this information on the basis of the marketing authorisation under Medicinal Products Act. For the designation, the G-BA, within the scope of its legislative discretion, uses the constellation of a "determined" or an "undetermined" combination as a justifiable interpretation variant.

If a designation as a so-called determined or as a so-called undetermined combination is omitted due to the lack of information on a combination therapy in the product information of the assessed medicinal product, the non-designation in the resolution according to Section 35a, paragraph 3, sentence 1 SGB V does not affect the possibility that the assessed medicinal product can be used in an open-label combination under marketing authorisation regulations.

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 SGBV.

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:

Adults, adolescents and children 6 years of age and above with genetically confirmed Bardet-Biedl syndrome (BBS) 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 and 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: 18 March 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

On 15 May 2023 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 15 August 2023 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 5 September 2023.

The oral hearing was held on 25 September 2023.

An amendment to the benefit assessment with a supplementary assessment was submitted on 13 October 2023.

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

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

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

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	8 August 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	19 September 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	25 September 2023	Conduct of the oral hearing
Working group Section 35a	4 October 2023 17 October 2023	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	24 October 2023	Concluding discussion of the draft resolution
Plenum	2 November 2023	Adoption of the resolution on the amendment of the AM-RL

Berlin, 2 November 2023

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

Prof. Hecken