Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 2 November 2023, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. **In Annex XII, the following information shall be added after No. 5 to the information on the benefit assessment of Setmelanotide in accordance with the resolution of 1 December 2022:**

Setmelanotide

Resolution of: 2 November 2023
Entry into force on: 2 November 2023
Federal Gazette, BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 2 September 2022):

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.

1. Extent of the additional benefit and significance of the evidence

Setmelanotide is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with 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.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

<u>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</u>

Extent of the additional benefit and significance of the evidence of setmelanotide:

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

Extent of the additional benefit and significance of the evidence of setmelanotide:

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↔	No relevant differences for the benefit assessment.
Health-related quality of life	n.a.	The data are not assessable.
Side effects	n.a.	The data are not assessable.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

RM-493-023 study: multicentre phase III study – 14-week randomised placebo-controlled treatment phase.

Mortality

No deaths occurred.

1 Data from the dossier assessment of the G-BA (published on 15. August 2023), and from the amendment to the dossier assessment from 13. Oktober 2023, unless otherwise indicated.

Morbidity

Endpoint	Setmelanotide N = 18[a]	Placebo N = 18[a]	Setmelanotide vs placebo Mean difference [95% CI]; p value
Change in body weight			
Body weight at baseline in kg (PCPB) Mean value (SD) Median (min; max)	 120.59 (29.91) 120.48 (61.1; 173.8)	 114.91 (26.77) 115.1 (70.7; 166)	
Body weight at study week 14 in kg Mean value (SD) Median (min; max)	 116.03 (28.7) 118.43 (67; 172)	 114.70 (26.89) 113.87 (68; 167.3)	
Change in body weight at study week 14 in kg Mean value (SD) Median (min; max)	 -4.55 (5.09) -3.53 (-7.09; -2.02)	 -0.21 (2.63) 0 (-7.5; 4.3)	-4.34 [-7.08; -1.59]; p = 0.0014[b]
Change in body weight at study week 14 in % Mean value (SD) Median (min; max)	 -3.66 (4.17) -2.94 (-13.2; 5.4)	 -0.23 (2.14) 0.01 (-1.30; 0.83)	-3.43 [-5.67; -1.19]; p = 0.0019[b]
Change in the BMI			
BMI at baseline (PCPB) in kg/m² Mean value (SD) Median (min; max)	 41.35 (10.02) 41.30 (24.4; 61.3)	 41.63 (10.06) 41.30 (24.6; 66.1)	
BMI at study week 14 (PCPB) in kg/m² Mean value (SD) Median (min; max)	 n.d.	 n.d.	
Change in BMI at study week 14 in kg/m² Mean value (SD) Median (min; max)	 -1.85 (1.56) -1.52 (-6.3; 0.7)	 -0.08 (1) -0.02 (-2.8; 1.4)	-1.77 [-2.57; -0.97]; p < 0.0001[c]
Change in setmelanotide vs placebo in % Mean value (SD) Median (min; max)	 -4.64 (4.07) -3.13 (-13.2; 2.8)	 -0.13 (2.3) -0.04 (-4.9; 3.2)	-4.51 [-6.52; -2.50]; p < 0.0001[c]

Endpoint	Setmelanotide N = 12	Placebo N = 10	Setmelanotide vs placebo Difference [95% CI]; p value
Change in BMI-z- in subjects under 18 years of age			
BMI-z at baseline (PCPB) in kg/m² Mean value (SD) Median (min; max)	 4.01 (1.417) 3.97 (1.8; 7.1)	 4.24 (2.02) 3.5 (2.4; 9.0)	
Change in BMI-z at study week 14 in kg/m² Mean value (SD) Median (min; max)	 -0.39 (0.238) -0.36 (-0.8; 0.1)	 -0.07 (0.143) 0.06 (-0.3; 0.1)	-0.32 [-0.5; -0.14][c] p = 0.0006[c]

Endpoint	Setmelanotide		
	Observed values based on the FAS (%)	Patients with event n (%)	[95% CI] p value
Body weight, ≥ 10% weight reduction at week 52 compared to baseline (ATB) (presented additionally)			
Weight reduction at week 52, n (%)	23 (82.1)[d]	10 (35.7)[d]	[18.6; 55.9] 0.0002[e]

Health-related quality of life

No data on the endpoint category of quality of life are available.

Side effects

Endpoint	Setmelanotide N = 22	Placebo N = 22	Setmelanotide vs placebo Effect estimator [95% CI]; p value
AE CTCAE grade ≥ 3, n (%)	0	0	n.d.[f]
SAE, n (%)	1 (4.5)	2 (9.1)	n.d.[f]
AEs which led to the discontinuation of the study medication, n (%)	0	2 (9.1)	n.d.[f]

a) All randomised subjects with at least one treatment with placebo or setmelanotide and available data at baseline (PCPB).
b) Difference calculated as setmelanotide - placebo. Based on the documents submitted, it is unclear whether the mean difference is based on Rubin's Rule. The 95% CI is based on the calculated difference if no data was missing. If imputation methods have been used, the 95% CI is based on Rubin's rule. The p value is based on Rubin's rule. The quantity of missing data is unclear. The use of Rubin's rule does not seem comprehensible in this context.
c) Calculation methodology not reported. According to the study report, the p value was calculated on an ad-hoc basis.

d) Percentage refers to the FAS of the pivotal cohort 12 years of age and above (N =28)
e) No clear information is available on the calculation of the p value.
f) No effect estimators were submitted with the dossier. Due to the number of events, no statistically significant difference between the treatment arms is assumed. A final assessment is not possible.

Abbreviations: BMI: Body Mass Index; CTCAE: Common Terminology Criteria for Adverse Events; FAS: full analysis set; n.d.: no data available; CI: confidence interval; N = number of patients evaluated; PCPB: placebo-controlled treatment phase; SD: standard deviation; (S)AE: (serious) adverse event; vs = versus.

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 300 – 1,100 patients

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.

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Children and adolescents aged 6 to ≤ 15 years	
Setmelanotide	€ 111,015.37 - € 333,046.11
Adolescents and adults 16 years of age and above	
Setmelanotide	€ 222,030.74 - € 333,046.11

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 October 2023)

Costs for additionally required SHI services: not applicable

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. 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.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 2 November 2023.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 2 November 2023

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

Prof. Hecken