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

of 1 December 2022

At its session on 1 December 2022, 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. Annex XII shall be amended in alphabetical order to include the active ingredient Setmelanotide as follows:

Setmelanotide

Resolution of: 1 December 2022
Entry into force on: 1 December 2022
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 16 July 2021):

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

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

See therapeutic indication according to marketing authorisation.

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 and older with POMC, PCSK1 or LEPR deficiency 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.

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

[1] Data from the dossier assessment of the G-BA (published on 1. September 2022), unless otherwise indicated.

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	↑	Advantage in the reduction of body weight and body mass index, respectively, at week 52 compared to baseline.
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
∅: There are no usable data for the benefit assessment.
n.c.: not calculable

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

012 and 015 studies: multicentre, single-arm phase III studies in patients ≥ 6 years with POMC/PCSK1- (012) or LEPR-deficiency obesity (015)

Mortality

Endpoint Study	Setmelanotide	
	N[b]	Patients with event n (%)
Overall mortality[a]		
012 015	15 15	0 (0) 1 (6.7)

Morbidity

Endpoint Study	Setmelanotide			
	N	Patients with event n (%)	[90% CI]	p value
Body weight, ≥ 10% weight reduction at week 52 compared to baseline				
012 015	14[c] 15[c]	12 (85.71) 8 (53.3)	[61.46, 97.40][d] [30.00, 75.63][d]	< 0.0001[e] < 0.0001[e]

Endpoint Study	**Setmelanotide**			
	N	Patients with event n (%)	[90% CI]	p value
	N	Patients (%)	Mean value (SD)	LS mean [90% CI] p value
BMI[f]				
012	13[f]			
Baseline		13 (100)[g]	37.80 kg/m^2 (7.67)	
Week 52		11 (84.61)[g]	27.57 kg/m^2 (4.88)	
Change at week 52		11 (84.61)[g]	-27.32% (8.97)	-27.7%[i] [-30.75; -24.65] < 0.0001
015	There are no assessable data.[g]			
BMI z score (age group < 18 years)				
012	There are no assessable data.[j]			
015	There are no assessable data.[j]			
	N	Patients with event n (%)	[90% CI]	p value
Hunger score (daily hunger questionnaire)[k] **Improvement of hunger by ≥ 25%** (age group ≥ 12 years) *(presented additionally)*				
012	14[c]			
Average hunger	9	5 (55.55)[l]	[28.92; 88.89][d]	< 0.0001[m]
Worst (most) hunger	9	4 (44.44)[l]	[19.29, 80.71][d]	< 0.0004[m]
Morning hunger	9	5 (55.55)[l]	[28.92, 88.89][d]	< 0.0001[m]
015	15[c]			
Average hunger	14	9 (64.29)[l]	[39.04; 84.73][d]	< 0.0001[m]
Worst (most) hunger	14	10 (71.43)[l]	[46.00; 89.60][d]	< 0.0001[m]
Morning hunger	14	9 (64.29)[l]	[39.04; 84.73][d]	< 0.0001[m]

Health-related quality of life

There are no assessable data.[n]

Side effects

Endpoint Study	**Setmelanotide**			
	N[b]	Patients with event n (%)		
Total adverse events (AEs) *(presented additionally)*				
012 015	15 15	15 (100.0) 15 (100.0)		
AE severity grade ≥ 3				
012 015	15 15	0 (0) 3 (20.0)[r]		
Serious adverse events (SAE)				
012 015	15 15	6 (40.0) 3 (20.0)		
AEs which led to the discontinuation of the study medication				
012 015	15 15	0 (0) 1 (6.7)		
	N[f]	Patients with event n (%)	Mean value (SD)	LS mean[p] [90% CI] p value
Depressiveness (using PHQ-9) Age group ≥ 12 years				
012	13			
Baseline		8 (61.54)[o]	6.9 (3.52)	
Week 52		8 (61.54)[o]	5.3 (4.37)	-21.09 [-55.83; 13.65] 0.1534
015	There are no assessable data.[q]			
Suicidality (using C-SSRS)				
012	There are no assessable data.[q]			
015	There are no assessable data.[q]			

a. Fatalities were recorded as part of the safety assessment.
b. The data are based on the safety population (SAS): Patients with any number of administrations of the study medication and with at least one examination of safety after administration of the study medication.
c. Analyses were carried out on the basis of data from all patients in the Full Analysis Set (FAS): Patients with at least one administration of the study medication and with at least one examination at baseline. Regardless of whether the patient achieved 5 kg weight loss (or 5% weight loss for patients with < 100 kg body weight at baseline) during the initial, open-label treatment phase of 12 weeks duration or was considered in the double-blind, placebo-controlled withdrawal phase. 012 study: N = 14; 015 study: N = 15.
d. Two-sided CI according to the Clopper-Pearson method.

e. One-sided p value resulting from an exact binomial test. Assumption that at least 5% of patients in the population of interest would achieve a 10% weight loss.
f. Analyses were based on the data of all patients on the Designated Use Set (DUS): Patients with any number of administrations of study medication for whom a weight loss of at least 5 kg (≥ 5% in patients < 100 kg body weight at the start of the study) was reported during the initial 12-week, open-label treatment phase and who were included in the subsequent double-blind, placebo-controlled withdrawal phase.
g. The percentage figures are based on own calculations and are based on DUS.
h. In the 015 study, the percentage of patients in the evaluation was below 70% in relation to the originally enrolled patients, which is why the results were not presented.
i. Model-based summary statistics from a mixed longitudinal analysis of variance model with fixed effect for week, baseline BMI and random effect for subject, one-sided p value from model.
j. For the age group < 18 years, the BMI z score was determined. Since only patient listings are available for the BMI z score, the data are not shown.
k. 11-point Likert scale; higher values mean a greater hunger.
l. The percentage figures are based on own calculations and are based on the FAS, taking into account the age group ≥ 12 years.
m. One-sided p value resulting from an exact binomial test. Assumption that at least 5% of patients in the population of interest would achieve ≥ 25% improvement in hunger.
n. The studies collected the IWQOL-Lite, SF-36 and PedsQL quality of life questionnaires. However, due to the low return rates at baseline and during the course of the study, or due to the lack of evaluations at the aggregate level, the data cannot be taken into account in the benefit assessment.
o. The percentage figures are based on own calculations and are based on DUS, without taking into account the age group ≥ 12 years.
p. Model-based summary statistics from a mixed longitudinal analysis of variance model with fixed effect for week, baseline PHQ-9 and random effect for subject, one-sided p value from model.
q. Too low return rates at baseline or during the course of the study, which is why the results were not presented.
r. According to documents subsequently submitted by the pharmaceutical company from the written statement procedure.

Abbreviations:
DUS = Designated Use Set; FAS = Full Analysis Set; IWQOL-Lite = Impact of Weight on Quality of Life Lite Version; CI = Confidence Interval; LS = Least Square; N = number of patients evaluated; n = number of patients with (at least one) event; PedsQL = Paediatric Quality of Life; PHQ-9 = Patient Health Questionnaire 9; SAS = Safety Analysis Set; SD = Standard Deviation; SF-36 = Short Form 36; SAE = Serious Adverse Event; AE= Adverse Event.

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

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

approx. 140 to 280 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: 7 November 2022):

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

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

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Children aged 6 to 11 years	
Setmelanotide	€ 58,159.65 - € 290,798.24
Adolescents and adults 12 years of age and above	
Setmelanotide	€ 116,319.30 - € 387,730.98

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 November 2022)

Costs for additionally required SHI services: not applicable

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

Medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V are medicinal products with the following new active ingredients that can be used in a combination therapy with setmelanotide for the treatment of obesity and control of the hunger in connection with POMC, PCSK1 or LEPR deficiency on the basis of the marketing authorisation under Medicinal Products Act:

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

No active ingredient that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 1 December 2022.

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

Berlin, 1 December 2022

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

Prof. Hecken