Gemeinsamer Bundesausschuss

Givosiran (Acute Hepatic Porphyria, ≥ 12 Years)

Resolution of: 15 October 2020 Valid: unlimited
Entry into force on: 15 October 2020
Federal Gazette, BAnz AT 14 01 2021 B2

Therapeutic indication (according to the marketing authorisation of 2 March 2020):

Givlaari® is indicated for the treatment of acute hepatic porphyria (AHP) in adults and adolescents aged 12 years and older.

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

Givosiran is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (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).

Patients 12 years and older with acute hepatic porphyria (AHP).

Extent of the additional benefit and significance of the evidence for givosiran:

Indication of a considerable additional benefit

Study results according to endpoints:[1]

Phase-III ENVISION study: Givosiran vs placebo (RCT study phase over 6 months), full analysis set (all randomised patients with ≥ 1 dose of the study medication)

Mortality

Endpoint	Givosiran	Placebo	Givosiran vs placebo
Mortality			
No deaths occurred.			

Morbidity

Endpoint	Givosiran		Placebo		Givosiran vs placebo
	N	*n* *[95% CI]*	N	*n* *[95% CI]*	*Rate Ratio*[1] *[95% CI]* *p value*
All porphyria attacks					
Number of attacks	48	109	46	317	0.32 [0.22; 0.47]; < 0.001
Annual attack rate[2]	48	4.34 [3.23; 5.83]	46	13.60 [10.66; 17.36]	
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	*Relative risk*[3] *[95% CI]* *p value*
Absence of attacks	48	18 (37.5)	48	6 (13.0)	3.11 [1.38; 7.01]; 0.003
	N	*n*	N	*n*	*Rate Ratio*[1] *[95% CI]* *p value*
Porphyria attacks requiring hospitalisation					
Number of attacks	48	50	46	69	0.57 [0.28; 1.15]; 0.1148
Porphyria attacks requiring emergency treatment					
Number of attacks	48	37	46	196	0.16 [0.08; 0.30]; < 0.001
Porphyria attacks requiring home administration of haemin (i.v.)					
Number of attacks	48	3	46	32	0.02 [0.00; 2.77]; 0.118

[1] Data from the dossier assessment by the G-BA (published on 15 July 2020) and from the amendment from 8 September 2020 to the dossier assessment unless indicated otherwise.

Endpoint	Givosiran		Placebo		Givosiran vs placebo
	N	*LS Mean (SEM)*	N	*LS Mean (SEM)*	*Mean difference[4] [95% CI] p value*
Pain intensity using Item 3 of the BPI-SF [5]					
Mean change between baseline and mean value of the weeks	48	−0.53 (0.19)	46	−0.01 (0.20)	−0.52 [−1.07; 0.03]; 0.0634
Fatigue using Item 3 of the BFI [6]					
Mean change between baseline and mean value of the weeks	48	−0.47 (0.19)	46	−0.16 (0.20)	−0.31 [−0.86; 0.24]; 0.2590
Nausea using NRS [7]					
Mean change between baseline and mean value of the weeks	48	0.07 (0.15)	46	−0.14 (0.15)	0.21 [−0.20; 0.62]; 0.3192
Endpoint	**Givosiran**		**Placebo**		**Givosiran vs placebo**
	N	*LS Mean (SEM)*	N	*LS Mean (SEM)*	*Mean difference[8] [95% CI] p value*
General health status using EQ-5D-VAS[9]					
Mean change between baseline and Month 6	48	5.0 (2.6)	46	−0.3 (2.7)	5.3 [−2.2; 12.8]; 0.1615
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	*Relative Risk[10] [95% CI]; p value*
General health status using PGI-C					
Improvement[11] at Month 6 since the start of study	48	33 (68.8)	46	14 (30.4)	2.31 [1.42; 3.76]; 0.0002
Deterioration[11] at Month 6 since the start of study	48	3 (6.3)	46	8 (17.4)	0.35 [0.10; 1.20], 0.0793

[1)] Rate ratio: Negative binomial regression. Adjusted for the stratification factors of AIP patients (i.e. use of haemin prophylaxis at the time of screening (yes vs no) and annual rate of porphyria attacks before the start of study (high vs low) as fixed effects). The logarithmic time (in years) of each study participant during the 6-

month treatment phase was included in the model as an offset variable
[2)] The annual attack rate is presented additionally to the number of attacks. It is calculated from the average annual attack rate determined for each patient (total number of porphyria attacks divided by the total number of days in the treatment period multiplied by 365.25).
[3)] Relative risk: Cochran-Mantel-Haenszel test
[4)] LS mean (difference): ANCOVA. Adjusted for the stratification factors of AIP patients (i.e. use of haemin prophylaxis at the time of screening (yes vs no) and annual rate of porphyria attacks before the start of study (high vs low) as fixed effects and mean value of the weeks to baseline as a covariate
[5)] Values between 0 (no pain) and 10 (worst pain imaginable)
[6)] Values between 0 (no fatigue) and 10 (worst fatigue imaginable)
[7)] Values between 0 (no nausea) and 10 (worst nausea imaginable)
[8)] LS mean (difference): MMRM adjusted for baseline value as continuous covariates and the stratification factors of AIP patients (i.e. use of haemin prophylaxis at the time of screening (yes vs no) and annual rate of porphyria attacks before the start of study (high vs low) as fixed effects)
[9)] Values between 0 (worst possible health status) and 100 (best possible health status)
[10)] Relative risk: Cochran-Mantel-Haenszel test. Category "improvement" compared with "all others" or "deterioration" compared with "all others". People with missing values were counted in the "all others" category
[11)] Any improvement or deterioration ("slight", "strong", and "very strong")

Abbreviations: AIP: acute intermittent porphyria; ALA: aminolevulinic acid; ANCOVA: Analysis of Covariance; BPI-SF: Brief Pain Inventory – Short Form; BFI: Brief Fatigue Inventory, EQ-5D-VAS: European Quality of Life 5 Dimensions Visual Analogue Scale; CI: confidence interval; LS: least squares, N: number of patients evaluated; PBG: Porphobilinogen; PGI-C: Patient Global Impression of Change; SD: standard deviation; SEM: Standard Error of the Mean

Health-related quality of life

Endpoint	**Givosiran**		**Placebo**		**Givosiran vs placebo**
	N	*LS Mean (SEM)*	N	*LS Mean (SEM)*	*Mean difference [95% CI] p value*
SF-12- Physical Component Summary[1]					
Mean change between baseline and Month 6	47	5.15 (1.16)	45	1.46 (1.19)	3.69[2] [0.41; 6.96]; 0.0280 *Hedges' g[3] [95% CI]* 0.46 [0.05; 0.88]
SF-12- Mental Component Summary[1]					
Mean change between baseline and Month 6	47	3.32[3] (1.32)	45	0.89[3] (1.36)	2.43[2.3] [−1.31; 6.17]; 0.1998

[1)] Values between 0 (worst possible quality of life) and 100 (best possible quality of life)
[2)] LS mean (difference): MMRM adjusted for baseline value as continuous covariates and the stratification factors of AIP patients (i.e. use of haemin prophylaxis at the time of screening (yes vs no) and annual rate of porphyria attacks before the start of study (high vs low) as fixed effects)
[3)] Information from back-calculation document for module 4 of the dossier because not available in the study report

Abbreviations: CI: confidence interval; LS: least squares, MMRM: Mixed Model Repeated Measures; N: number of patients evaluated; SD: standard deviation; SEM: Standard Error of the Mean; SF-12: Short Form 12

Side effects

Endpoint	Givosiran		Placebo		Givosiran vs placebo
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Effect estimator [95% CI] p value
Adverse events (AE)					
	48	43 (89.6)	46	37 (80.4)	–[1]
Serious adverse events (SAE)					
	48	10 (20.8)	46	4 (8.7)	2.23 [0.79; 6.29]; 0.115[3]
Severe adverse events[2]					
	48	8 (16.7)	46	5 (10.9)	1.41 [0.51; 3.94]; 0.507[3]
Therapy discontinuations because of AE					
	48	1 (2.1)[4]	46	0	n.a.
Discontinuation of the study medication because of AE					
	48	1 (2.1)[4]	46	0	n.a.
AE of any grade with incidence ≥ 10% in one study arm and a difference ≥ 10% between the study arms					
MedDRA[5] system organ class, preferred term					
Gastrointestinal disorders	48	20 (41.7)	46	19 (41.3)	1.03 [0.64; 1.68]; p = 0.899[6]
Nausea	48	13 (27.1)	46	5 (10.9)	2.62 [1.03; 6.65]; p = 0.033[6]
General disorders and administration site conditions	48	21 (43.8)	46	14 (30.4)	1.41 [0.83; 2.41]; p = 0.201[6]
Fever	48	1 (2.1)	46	6 (13.0)	n.c.
Reaction at the injection site	48	8 (16.7)	46	0	n.c.
Renal and urinary disorders	48	7 (14.6)	46	2 (4.3)	n.c.
Chronic kidney disease	48	5 (10.4)	46	0	n.c.

[1] Patient relevance of laboratory parameters unclear.
[2] Includes AE with severity “severe” and no indication of severity.
[3] Relative risk: Cochran-Mantel-Haenszel test. Information from back-calculation document for module 4 of the dossier because not available in the study report.
[4] Deviating information in Module 4 of the dossier: It is stated that no person discontinues the study because of AE.

[5] MedDRA Version 21.0.
[6] Relative risk: Cochran-Mantel-Haenszel test. Information from Module 4 of the dossier of the pharmaceutical company.

Abbreviations: CI: confidence interval; N: number of patients evaluated; n: Number of patients with (at least one) event; n.c.: not calculable vs: versus

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑↑	Advantage in acute porphyria attacks, advantage in health status
Health-related quality of life	↔	No differences relevant for the benefit assessment
Side effects	↔	No differences relevant for the benefit assessment

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.a.: not assessable

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

approx. 1,000 to 1,700 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 Givlaari® (active ingredient: givosiran) at the following publicly accessible link (last access: 29 July 2020):
https://www.ema.europa.eu/en/documents/product-information/givlaari-epar-product-information_de.pdf

Treatment with givosiran should only be initiated and monitored by physicians who are experienced in the treatment of patients with acute hepatic porphyria.

4. Treatment costs

Annual treatment costs:

Patients 12 years and older with acute hepatic porphyria (AHP).

Designation of the therapy	Annual treatment costs/patient
Givosiran	€ 621,350.04 – 1,242,700.08

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 September 2020

Costs for additionally required SHI services: not applicable