Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Betibeglogene Autotemcel (β-Thalassaemia)

of 14 May 2020

At its session on 14 May 2020, the Federal Joint Committee (G-BA) resolved to amend the Directive on the Prescription of Medicinal Products in SHI-accredited Medical Care (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 on DD 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 betibeglogene autotemcel as follows:

Betibeglogene autotemcel

Resolution of: 14 May 2020
Entry into force on: 14 May 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 29 May 2019):

Zynteglo is indicated for the treatment of patients 12 years and older with transfusion-dependent β-thalassaemia (TDT) who do not have a β 0 /β 0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available (see sections 4.4 and 5.1).

1. Extent and probability of the additional benefit of the medicinal product

Betibeglogene autotemcel is approved as a medicinal product for the treatment of rare diseases in accordance with 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 transfusion-dependent β-thalassaemia (TDT) who do not have a β 0 /β 0 genotype, for whom haematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Extent of the additional benefit and the significance of the proof for betibeglogene autotemcel:

Hint for a non-quantifiable additional benefit owing to the fact that the scientific data does not permit quantification

Study results according to endpoints:[1]

Study HGB-207 and HGB-212: Non-controlled phase III study

Studies HGB-205 and HGB-204: Non-controlled phase I/II dose-finding studies

Relevant sub-populations: Patients of > 12 years with transfusion-dependent β-thalassaemia (TDT) who do not have a β 0 /β 0 genotype

[1] Data from the dossier evaluation of the G-BA (published on 17 February 2020) and the amendment of the dossier evaluation of 7 April 2020

Mortality

Endpoint	Betibeglogene autotemcel	
	N	*Patients with event n (%)*
Mortality		
No fatalities occurred in any of the four studies		

Morbidity

Endpoint[1]	Betibeglogene autotemcel			
	N[2]	*Patients with event n (%)*		
Transfusion independence, TI				
HGB-207	15	13 (86.7)		
HGB-205	4	3 (75.0)		
HGB-204	10	8 (80.0)		
HGB-212	4	1 (25.0)		
	N[3]	*Median (min.; max.)*		
Observation time with TI[4,5,6] (months), additionally shown for study participants achieving TI				
HGB-207	13	19.20 (12.2; 27.0)		
HGB-205	3	56.30 (38.2; 57.6)		
HGB-204	8	44.75 (28.3; 51.3)		
HGB-212	1	12.20 (12.2; 12.2)		
	N[2]	*n (%)*	*Mean (SD)*	*<u>Change from baseline</u> Mean (SD)*
VAS from EQ-5D[7] (≥ 18 years), 12 months				
HGB-207	15	7[8] (77.7)	91.29 (6.32)	7.29 (10.44)
VAS from EQ-5D-Y[7] (≥ 12 and ≤ 17 years), 6 months				
HGB-207	15	6[9] (100)	93.3 (4.45)	24.5 (20.8)

1) Collected on 12 June 2019. For studies HGB-205 and HGB-204, the final data including the second interim data cut-off of the long-term follow-up for study LTF-303 were available. For studies HGB-207 and HGB-212, data were available for the transfusion independence endpoint from the interim data cut-off of 2 December 2019.
2) Based on the transplant population
3) Based on patients of the transplant population who achieved transfusion independence
4) Calculation of the duration of TI was performed under the assumption that TI ceased at the time of the last assessment of the Hb value. In reality, the maximum duration of TI is unknown and exceeds the duration from t_0 until the time of the last assessment of the Hb value.
5) In the analysis of the transfusion independence endpoint, all study participants were considered who had already achieved the definition of TI at the time of data extraction, were no longer able to achieve it in the further course of the original study, or had completed the study protocol at month 24 of the original study.

[6] TI is defined as a continuous period of at least 12 months without receiving transfusions of erythrocyte concentrates and a weighted mean Hb concentration of ≥ 9 g/dl at any time after the infusion of Zynteglo and ceases at the end of the observation period.
[7] Scale from 0–100, a higher value corresponds to a better health status.
[8] Return rate based on study participants aged ≥ 18 years; in total 9 patients in the transplant population were over 18 years of age.
[9] Return rate based on study participants aged ≥ 12 to ≤ 18 years; in total 6 patients in the transplant population were under 18 years of age.

Abbreviations: EQ-5D(-Y): EuroQol 5-dimension questionnaire (youth); ITT: intention to treat, SD: Standard deviation;; TDT: transfusion-dependent β-thalassaemia; TI: transfusion independence; VAS: visual analogue scale

Health-related quality of life

Endpoint[1]	Betibeglogene autotemcel			
	N[2]	*n (%)*	*Mean (SD)*	*Change from baseline Mean (SD)*
PedsQL – total score[3,6], 6 months				
HGB-207	15	6[4] (100)	80.98 (13.93)	9.96 (24.30)
SF-36 – PCS[3], 12 months				
HGB-207	15	7[5] (77.7)	55.75 (3.86)	2.72 (2.81)
SF-36 – MCS[3], 12 months				
HGB-207	15	7[5] (77.7)	50.20 (7.75)	1.61 (9.41)
FACT-G total score, 12 months				
HGB-207	15	7[5] (77.7)	97.95 (6.12)	4.62 (14.22)

[1] Collected on 12 June 2019. For HGB-207, these are the interim data cut-off figures.
[2] Based on the transplant population
[3] Scale from 0–100, a higher value corresponds to a better health status.
[4] Return rate based on study participants aged ≥ 12 to ≤ 18 years; in total 6 patients in the transplant population were under 18 years of age.
[5] Return rate based on study participants aged ≥ 18 years; in total 9 patients in the transplant population were over 18 years of age.
[6] Assessment by patients.

Abbreviations: FACT-BMT: Functional Assessment of Cancer Therapy – Bone Marrow Transplant; FACT-G: Functional Assessment of Cancer Therapy – General; MCS: Mental Component Summary score; PedsQL: Paediatric Quality of Life Inventory; PCS Physical Component Summary score; SF-36 36-Item Short Form Health Survey; SD: standard deviation

Side effects

Endpoint	Betibeglogene autotemcel		
	Patients with event n (%)		
	HGB-207 N = 16[1]	HGB-205 N = 4[1]	HGB-204 N = 11[1]
Adverse events (AE) in total	16 (100)	4 (100)	10 (90.9)
Severe AEs (CTCAE grade ≥ 3), n (%)	15 (93.8)	4 (100)	10 (90.9)
Serious adverse events (SAE)	9 (56.3)	3 (75.0)	6 (54.5)
AEs that led to withdrawal from the study	0	0	0
Severe AE grade CTCAE ≥ 3 with an incidence of ≥ 5 %, MedDRA system organ class, preferred term			
Blood and lymphatic system disorders	15 (93.8)	4 (100)	10 (90.9)
Thrombocytopoenia	15 (93.8)	4 (100)	10 (90.9)
Anaemia	10 (62.5)	4 (100)	7 (63.6)
Neutropoenia	11 (68.8)	4 (100)	6 (54.5)
Leukopoenia	10 (62.5)	0	5 (45.5)
Febrile neutropoenia	3 (18.8)	0	6 (54.5)
Gastrointestinal disorders	9 (56.3)	4 (100)	9 (81.8)
Stomatitis	9 (56.3)	4 (100)	8 (72.7)
Diarrhoea	1 (6.3)	0	1 (9.1)
General disorders and administration site conditions	6 (37.5)	0	0
Mucosa inflammation	2 (12.5)	0	0
Fever	3 (18.8)	0	0
Fatigue	2 (12.5)	0	0
Hepatobiliary disorders	3 (18.8)	0	1 (9.1)
Hepatic disorder with vein occlusion	3 (18.8)	0	1 (9.1)
Infections and infestations	5 (31.3)	1 (25.0)	3 (27.3)

Endpoint	Betibeglogene autotemcel		
	Patients with event n (%)		
	HGB-207 N = 16[1]	HGB-205 N = 4[1]	HGB-204 N = 11[1]
Neutropoenic sepsis	2 (12.5)	0	0
Injury, poisoning and procedural complications	1 (6.3)	1 (25.0)	2 (18.2)
Investigations	3 (18.8)	2 (50.0)	0
Increased aspartate aminotransferase	1 (6.3)	2 (50.0)	0
Increased alanine aminotransferase	1 (6.3)	1 (25.0)	0
Blood bilirubin increased	2 (12.5)	0	0
Metabolism and nutrition disorders	1 (6.3)	1 (25.0)	1 (9.1)
Hypophosphataemia	1 (6.3)	1 (25.0)	0
Reproductive system and breast disorders	1 (6.3)	1 (25.0)	3 (27.3)
Irregular menstruation	1 (6.3)	0	3 (27.3)
Respiratory, thoracic and mediastinal disorders	5 (31.3)	0	2 (18.2)
Epistaxis	3 (18.8)	0	0
Pharyngeal inflammation	1 (6.3)	0	2 (18.2)
Hypoxia	2 (12.5)	0	0
Vascular disorders	1 (6.3)	0	1 (9.1)
Hypotonia	1 (6.3)	0	1 (9.1)
SAEs with incidence of ≥ 5 %, MedDRA system organ class, preferred term			
Blood and lymphatic system disorders	2 (12.5)	0	1 (9.1)
Thrombocytopoenia	2 (12.5)	0	0
Hepatobiliary disorders	3 (18.8)	0	1 (9.1)
Hepatic disorder with vein occlusion	3 (18.8)	0	1 (9.1)
Infections and infestations	3 (18.8)	2 (50.0)	3 (27.3)

Endpoint	Betibeglogene autotemcel		
	Patients with event n (%)		
	HGB-207 N = 16[1]	HGB-205 N = 4[1]	HGB-204 N = 11[1]
Injury, poisoning and procedural complications	2 (12.5)	1 (25.0)	1 (9.1)
Metabolism and nutrition disorders	1 (6.3)	1 (25.0)	0
Vascular disorders	1 (6.3)	0	1 (9.1)

[1)] ITT population (population compliant with marketing authorisation)

Abbreviations: ITT: Intention to treat; MedDRA: Medical Dictionary for Regulatory Activities; SAE(s): serious adverse event(s), TDT; transfusion-dependent β-thalassaemia, AE(s): adverse event(s).

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ Risk of bias	Summary
Mortality	n.a.	No deaths occurred
Morbidity	↑	Benefit in the transfusion independence endpoint
Health-related quality of life	n.a.	No comparative data on quality of life were provided.
Side effects	n.a.	No comparative data on side effects were provided.

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. 50 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 Zynteglo® (active ingredient: betibeglogene autotemcel) at the following publicly accessible link (last access: 30 April 2020):

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

Under the terms of marketing authorisation, treatment with Zynteglo may only be carried out in qualified treatment facilities and must be initiated and monitored by doctors who are experienced in transplantation of haematopoietic stem cells and treatment of patients with transfusion-dependent β-thalassaemia.

Regarding additional measures for risk minimisation, the pharmaceutical company must provide officially approved training material for medical personnel and an information package including a patient identification card for patients.

As per the German FI, patients are expected to enrol in a registry and participate in long-term follow-up within the registry to improve understanding of the long-term safety and efficacy of Zynteglo.

This medicinal product was approved under "special conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The EMA will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

The regulations under Section 35a paragraph 3b and Section 136a paragraph 5 SGB V remain unaffected by this.

4. Treatment costs

Annual treatment costs:

Designation of the therapy	Annual treatment costs/patient
Betibeglogene autotemcel[2]	€ 1,874,250
Additionally required SHI services	€ 5,687.94–8,531.91

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

[2] Because HSC mobilisation and leukapheresis are involved in the manufacture of the medicinal product under Section 4 paragraph 14 AMG, no further costs are incurred in this respect for the medicinal product to be assessed.

Other services covered by SHI funds:

Designation of the therapy	Type of service	Costs/ unit	Number/ cycle	Number/ patient/ year	Costs/ patient/ year
Busulfan	Surcharge for production of a parenteral preparation containing cytostatic agents	€ 81	4–16	4–16	€ 324 – € 1,296

II. Entry into force

1. **The resolution will enter into force on the day of its publication on the internet on the website of the G-BA on 14 May 2020.**
2. **The period of validity of the resolution is limited to 15 May 2025.**

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

Berlin, 14 May 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken