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 Bedaquiline (New Therapeutic Indication: pulmonary multidrug-resistant tuberculosis, 5 to 11 years)

of 16 September 2021

At its session on 16 September 2021, 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 TT. Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. In Annex XII, the following information on the benefit assessment of bedaquiline as set out in the resolution of 20. August 2020 is added after no. 4:

Bedaquiline

Resolution of: 16 September 2021
Entry into force on: 16 September 2021
BAnz AT DD. MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 29 March 2021):

Sirturo is indicated for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult and paediatric patients (5 years to less than 18 years of age and weighing at least 15 kg) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

Therapeutic indication of the resolution (resolution of 16 September 2021):

Sirturo is used in paediatric patients (**aged 5 years to less than 12 years** and weighing at least 15 kg) as part of an appropriate combination therapy for multidrug-resistant pulmonary tuberculosis (MDR-TB) when an effective treatment regimen cannot be otherwise composed due to resistance or intolerance.

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

Bedaquiline 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. In accordance with 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).

<u>Children (aged 5 years to less than 12 years and weighing at least 15 kg) with multidrug-resistant pulmonary tuberculosis when an effective treatment regimen cannot be otherwise composed due to resistance or intolerance with the exception of bedaquiline (as part of appropriate combination therapy)</u>

Extend of the additional benefit and significance of the evidence of bedaquiline:

In conclusion, there is a hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

Children (aged 5 years to less than 12 years and weighing at least 15 kg) with multidrug-resistant pulmonary tuberculosis when an effective treatment regimen cannot be otherwise composed due to resistance or intolerance with the exception of bedaquiline (as part of appropriate combination therapy)

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	n.a.	The data are not assessable.
Morbidity	n.a.	The data are not assessable.
Health-related quality of life	∅	No data on quality of life are available.
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.a.: not assessable		

C211 study: Phase II, single-arm, open-label, multicentre study to evaluate the pharmacokinetics, safety, tolerability, and anti-mycobacterial efficacy of bedaquiline. Representation of the relevant sub-population of children aged ≥ 5 to < 12 years (cohort 2) at week 24 (data cut-off 10.01.2019)

Mortality

C211 study Endpoint[a]	Bedaquiline + BR	
	N	Patients with event n (%)
Overall survival		
No deaths occurred.		

Morbidity

[1] Data from the dossier assessment of the G-BA (published on 1. Juli 2021), and from the amendment to the dossier assessment from 12. August 2021), unless otherwise indicated.

C211 study Endpoint[a]	Bedaquiline + BR	
	N	Patients with event n (%)
Clinical TB symptomatology subsiding[f]		
Completely subsided Partially subsided Not subsided Missing	13[b] 13[b] 13[b] 13[b]	10 (76.9) 1 (7.7) 1 (7.7) 1 (7.7)
Absence of pathogens in the sputum (presented additionally)		
Subjects with MGIT-evaluable samples[d]	15[c]	3 (20.0)
Confirmed absence of pathogens in the sputum[e] Subjects with a confirmed absence of pathogens in the sputum	15[c]	3 (20.0)

Health-related quality of life

C211 study Endpoint[a]	Bedaquiline + BR	
	N	Patients with event n (%)
Not surveyed		

Side effects

C211 study Endpoint[a]	Bedaquiline + BR	
	N	Patients with event n (%)
Adverse events (AEs)		
	15[c]	-
Serious adverse events (SAE)		
	15[c]	2 (13.3)
Severe adverse events (CTCAE grade 3 or 4)		
AE of severity ≥ 3	15[c]	8 (53.3)
Therapy discontinuation due to adverse events		
AE, which led to the discontinuation of bedaquiline therapy	15[c]	3 (20.0)
AE, which led to the discontinuation >1 medicinal products of the base therapy	15[c]	4 (26.7)
AEs of special interest		
Drug-induced liver diseases - comprehensive search (SMQ)	15[c]	8 (53.3)
Liver failure, fibrosis and cirrhosis and other diseases caused by liver damage (SMQ)	15[c]	3 (20.0)

C211 study Endpoint[a]	Bedaquiline + BR	
	N	Patients with event n (%)
Hepatotoxicity	15[c]	3 (20.0)
Liver-related investigations, signs and symptoms (SMQ)	15[c]	2 (13.3)
Alanine aminotransferase increased	15[c]	2 (13.3)
Elevated aspartate aminotransferase	15[c]	2 (13.3)
Liver-related coagulation and bleeding disorders (SMQ)	15[c]	5 (33.3)
Prothrombin time prolonged	15[c]	5 (33.3)
Acute pancreatitis	15[c]	0 (0.0)
Rhabdomyolysis/myopathy	15[c]	0 (0.0)
Severe AE of the skin	15[c]	0 (0.0)
Torsades de Pointes / QT prolongation	15[c]	0 (0.0)
Persistent haematuria	15[c]	0 (0.0)
Persistent haematuria and deterioration of renal function	15[c]	0 (0.0)

a) The results presented are for the total treatment period and take into account events that occurred during the 24-week bedaquiline treatment period and/or during the follow-up period while continuing treatment with the base therapy up to the 10.01.2019 data cut-off.

b) mITT population: All subjects in the ITT population with confirmed or probable MRD-TB. 2 subjects in the ITT population were not included in the mITT population: 1 subject due to infection with non-tuberculous mycobacteria and 1 subject due to sensitivity to rifampicin.

c) ITT population: All subjects who have received at least one dose of bedaquiline.

d) Patients had a positive culture at baseline or screening, and there was at least one MGIT result at post-baseline.

e) Confirmed absence of pathogens was defined in study C211 as 2 consecutive negative microbiological cultures from sputum or other microbiological specimens obtained at least 25 days apart within the analysis time window.

f) The endpoint was collected by medical investigators in the study.

Abbreviations:

BR: Base therapy; ITT: Intention-to-Treat; TB: Tuberculosis; CI: Confidence interval; M=F: Missing=Failure; MGIT: Mycobacteria Growth Indicator Tube; mITT: modified intention-to-treat; NR: not reached; SMQ: Standardised MedDRA Query; SAE: serious adverse event; AE: adverse event

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

Children (aged 5 years to less than 12 years and weighing at least 15 kg) with multidrug-resistant pulmonary tuberculosis when an effective treatment regimen cannot be otherwise composed due to resistance or intolerance with the exception of bedaquiline (as part of an appropriate combination therapy)

approx. 1 patient

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 Sirturo (active ingredient: bedaquiline) at the following publicly accessible link (last access: 22 July 2021):

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

Treatment with bedaquiline should only be initiated and monitored by doctors experienced in treating patients with MDR-TB.

It is recommended that bedaquiline (Sirturo) be used under directly observed therapy (DOT).

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

Children and adolescents weighing between 30 and 40 kg are expected to have a higher average exposure compared to adult patients. This could be associated with an increased risk of QT prolongation or hepatotoxicity.

4. Treatment costs

Annual treatment costs:

Children (aged 5 years to less than 12 years and weighing at least 15 kg) with multidrug-resistant pulmonary tuberculosis when an effective treatment regimen cannot be otherwise composed due to resistance or intolerance with the exception of bedaquiline (as part of appropriate combination therapy)

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Bedaquiline	€ 13,149.88 - € 29,739.04

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 September 2021)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 16 September 2021.

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

Berlin, 16 September 2021

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

Prof. Hecken