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 Bedaquiline (New Therapeutic Indication: Multi-drug-resistant Pulmonary Tuberculosis, 12 to < 18 years)

of 20 August 2020

At its session on 20 August 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 bedaquiline as follows:

Bedaquiline

Resolution of: 20 August 2020
Entry into force on: 20 August 2020
Federal Gazette, BAnz AT DD MM YYYY Bx

New therapeutic indication (according to the marketing authorisation of 27 January 2020):

Situro is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug-resistant tuberculosis [multi-drug-resistant *Mycobacterium tuberculosis* (MDR-TB)] in adults and adolescent patients (12 years to less than 18 years of age and weighing at least 30 kg) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. Consideration should be given to official guidance on the appropriate use of antibacterial agents.

This resolution relates exclusively to the newly approved therapeutic indication of adolescent patients (12 years to less than 18 years of age and weighing at least 30 kg) with multi-drug-resistant pulmonary tuberculosis (MDR-TB), when an effective treatment regimen other than bedaquiline (as part of an appropriate combination regimen) cannot be composed for reasons of resistance or tolerability.

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

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. 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).

Adolescent patients (12 years to less than 18 years of age and weighing at least 30 kg) with multi-drug-resistant *pulmonary tuberculosis* (MDR-TB), when an effective treatment regimen other than bedaquiline (as part of an appropriate combination regimen) cannot be composed for reasons of resistance or tolerability.

Extent of the additional benefit and the significance of the proof for bedaquiline:

Hint for a non-quantifiable additional benefit because the scientific data does not permit quantification.

Study results according to endpoints:[1]

C211 study: Single arm, open-label, multi-centre Phase II study to investigate the pharmacokinetics, safety, tolerability, and anti-mycobacterial efficacy of bedaquiline. Presentation of the relevant sub-population of adolescents from ≥ 12 to < 18 years (Cohort 1) at week 24 (data cut-off of 14 November 2017)

Mortality

Study C211 **Endpoint**	**Bedaquiline + BR** Patients with event n (%)
Mortality	
No deaths occurred.	

Morbidity

Study C211 **Endpoint**	**Bedaquiline + BR** **ITT population** **N = 15**
Morbidity	
Remission of clinical TB symptomatology [a]	
Persons surveyed for the endpoint, n (%) Completely resolved Partially resolved Not resolved	14 (93.3) [b, c] 7 (46.7) [d] 7 (46.7) [d] 0 (0.0) [c]
Absence of pathogens in sputum	
Persons with MGIT evaluable samples [e], n (%)	8 (53.3)
Confirmed absence of pathogens in sputum [f] Persons with a confirmed absence of pathogens in sputum, n (%) Time until absence of pathogens in sputum (in days) [95% CI] [g, h]	 6 (40.0) 55 [29; NE]
No confirmed absence of pathogens in sputum, n (%) Persons without confirmed absence of pathogens in sputum Discontinuation of the study with the status “not converted” No conversion	 2 (13.3) 1 (6.7) 1 (6.7)

[a] The endpoint is determined by the investigator.
[b] One person discontinued the study prematurely, which is why results are available for 14 people at Week 24.
[c] In module 4, the results are presented according to the “primary absence = failure method”, which is why results are available for all 15 persons participating in the study (n = 15). Missing values because of the discontinuation of studies are assessed as “TB symptomatology has not subsided”. In the study, this applies to one patient (“not subsided”: n = 1 (6.7%)). The presentation was made exclusively for the dossier, module 4.
[d] Own calculation of the percentage of patients per category in relation to the ITT population (N=15).
[e] At baseline, 8 of the 11 people with confirmed MDR-TB had positive MGIT samples.
[f] Confirmed absence of pathogens in sputum defined as two consecutive negative microbiological cultures from the sputum taken at least 25 days apart.

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

[g] Time until confirmed absence of pathogens in sputum defined as the time interval (in days) from the first intake of the study medication (bedaquiline together with the base therapy) to the date of the first of two consecutive negative microbiological cultures from the sputum (confirmed absence of pathogens) taken at least 25 days apart
[h] Imputation method: M=F (missing values are counted as failure).
Abbreviations: BR: Base therapy; ITT - intention to treat, TB: tuberculosis; CI: confidence interval; M=F: Missing=Failure; MGIT: Mycobacteria Growth Indicator Tube; NA: not achieved

Health-related quality of life

Study C211 **Endpoint**
not collected

Side effects

Study C211 **Endpoint**	**Bedaquiline + BR [a, b]** **ITT population** **N = 15** Patients with event n (%)
Adverse events	
AE	14 (93.3)
AE Severity ≥ 3 [c,d]	4 (26.7)
Serious adverse events (SAE)	
SAE	2 (13.3)
AE of special interest SMQ term Sub SMQ term Term	
Any AE of special interest	5 (33.3)
Acute pancreatitis	1 (6.7)
Increased bilirubin concentration in the blood	1 (6.7)
Drug-induced liver disorders (comprehensive search)	4 (26.7)
Liver-induced investigations: Signs and symptoms	1 (6.7)
Alanine aminotransferase increased	1 (6.7)
Aspartate aminotransferase increased	1 (6.7)
Bilirubin concentration in the blood increased	1 (6.7)
Liver-induced coagulation and bleeding disorders	3 (20.0)
Prothrombin time prolonged	3 (20.0)
Severe skin events	1 (6.7)
Conjunctivitis	1 (6.7)
Therapy discontinuation because of adverse events	
AE that led to discontinuation of the bedaquiline therapy	0 (0.0)

AE that led to discontinuation of one of the anti-TB medicinal products	5 (33.3)

[a] The treatment phase includes a 24-week treatment with bedaquiline + BR. The median observation period was 23.9 weeks (min; max: 20; 25).
[b] The results of the entire study duration up to the data cut-off of 14 November 2017 include the 24-week treatment phase with bedaquiline + BR and the subsequent follow-up phase with the base therapy. The median observation time was 42.0 weeks (min; max: 20; 78). Depending on the time of study inclusion, different observation periods of the study participants are included in the evaluation. The results correspond to the 24-week treatment phase with bedaquiline + BR.
[c] Severity classification (if applicable) according to DMID toxicity tables or (if not applicable) abnormal test results (below/above normal values)
[d] The results of the CTCAE assessment in Module 4 correspond to the results of the a priori predefined severity classification according to DMID. Severity of thyroid dysfunction, hearing loss, arthralgia and arthritis are assessed according to the "Consensus Statement on Research Definitions for Drug-Resistant Tuberculosis in Children des Sentinel Project on Pediatric Drug-Resistant Tuberculosis" because these are not covered by the DMID.
Abbreviations used:
Abbreviations: BR: base therapy; ITT: intention to treat, SMQ: standardised MedDRA questionnaire; (S)AE: (serious) adverse event(s)

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	∅	There are no data on quality of life.
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

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

Adolescent patients (12 years to less than 18 years of age and weighing at least 30 kg) with multi-drug-resistant *pulmonary tuberculosis* (MDR-TB), when an effective treatment regimen other than bedaquiline (as part of an appropriate combination regimen) cannot be composed for reasons of resistance or tolerability.

approx. 9–13 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 Sirturo® (active ingredient: bedaquiline) at the following publicly accessible link (last access: 4 June 2020):
https://www.ema.europa.eu/documents/product-information/sirturo-epar-product-information_en.pdf

Treatment with bedaquiline should be initiated and monitored only by specialists who are experienced in the treatment of patients with MDR-TB.

It is recommended that directly observed therapy (DOT) be used as a strategy when administering bedaquiline (Sirturo).

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.

Adolescents with a body weight between 30 and 40 kg are expected to have a higher average exposure than adult patients. This could be associated with an increased risk of QT prolongation or hepatotoxicity.

4. Treatment costs

Annual treatment costs:

Adolescent patients (12 years to less than 18 years of age and weighing at least 30 kg) with multi-drug-resistant *pulmonary tuberculosis* (MDR-TB), when an effective treatment regimen other than bedaquiline (as part of an appropriate combination regimen) cannot be composed for reasons of resistance or tolerability.

Designation of the therapy	Annual treatment costs/patient
Bedaquiline	€ 28,988.96

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

Costs for additionally required SHI services: not applicable

II. **The resolution will enter into force with effect from the day of its publication on the internet on the website of the G-BA on 20 August 2020.**

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

Berlin, 20 August 2020

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

Prof. Hecken