Bedaquiline (reassessment after the deadline: pulmonary multidrug-resistant tuberculosis) – naming of concomitant active ingredients

Resolution of: 1 February 2024/7 August 2025 Valid until: unlimited
Entry into force on: 1 February 2024/7 August 2025
Federal Gazette, BAnz AT 25 04 2024 B2/ BAnz AT 02 10 2025 B2

Therapeutic indication (according to the marketing authorisation of 5 March 2014):

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. Consideration should be given to official guidelines on the appropriate use of antibacterial agents.

Therapeutic indication of the resolution (resolution of 1 February 2024):

Treatment of pulmonary multidrug-resistant tuberculosis (MDR-TB) in adults as part of an appropriate combination therapy when an effective treatment regimen cannot otherwise be composed for reasons of resistance or intolerance.

1. Extent 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 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).

Adult patients with pulmonary multidrug-resistant tuberculosis for whom an effective treatment regimen cannot be composed other than with bedaquiline (as part of an appropriate combination therapy) for reasons of resistance or intolerance

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

Hint for a considerable additional benefit.

Study results according to endpoints:[1]

Adult patients with pulmonary multidrug-resistant tuberculosis for whom an effective treatment regimen cannot be composed other than with bedaquiline (as part of an appropriate combination therapy) for reasons of resistance or intolerance

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment.
Morbidity	↑	Advantage in the endpoint of cure.
Health-related quality of life	∅	No data available.
Side effects	↔	No relevant differences 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 ∅: No data available. n.a.: not assessable		

TMC207-C208 study (C208): Phase II RCT comparing bedaquiline + base therapy (BR)[m] vs placebo + BR[m] at week 120 (ITT population) – data cut-off from 31.01.2012 (for morbidity and side effects) and 16.10.2012 (for mortality)

Mortality

C208 study Endpoint	Bedaquiline/ BR[m]		Placebo/ BR[m]		Bedaquiline/ BR vs Placebo/ BR
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR[d,e,f] [95% CI] p value[g]
Mortality[a,b,c]					
Overall mortality	79	n.r. [34.6; n.r.] *10 (12.7)*	81	n.r. [38.6; n.r.] *3 (3.7)*	3.23 [0.85; 12.27]; 0.130

[1] Data from the dossier assessment of the G-BA (published on 1. November 2023), unless otherwise indicated.

Morbidity

C208 study Endpoint	Bedaquiline/ BR[m]		Placebo/ BR[m]		Bedaquiline/ BR vs Placebo/ BR
	N	Patients with event n (%)	N	Patients with event n (%)	RR[f,i,j] [95% CI] p value[i]
Morbidity[h]					
Cure (WHO 2008)	79	45 (57.0)	81	27 (33.3)	1.67 [1.17; 2.38]; 0.006
Relapses (presented additionally)	*79*	*6 (7.6)*	*81*	*11 (13.6)*	*0.56 [0.22; 1.44] p = 0.23*

C208 study Endpoint	Bedaquiline/ BR[m]		Placebo/ BR[m]		Bedaquiline/ BR vs Placebo/ BR
	N	Median in days (IQR) [95% CI] *Patients with event n (%)*	N	Median in days (IQR) [95% CI] *Patients with event n (%)*	HR[d,f] [95% CI] p value[g]
Morbidity[h]					
Absence of pathogens in the sputum (presented additionally)	*79*	*86 [70; 112] 48 (60.8)*	*81*	*345 [140; n.a.] 37 (35.7)*	*2.01 [1.29; 3.14] p = 0.003*

Health-related quality of life

No data on the endpoint category of quality of life are available.

Side effects

C208 study Endpoint	Bedaquiline/ BR[m]		Placebo/ BR[m]		Bedaquiline/ BR vs Placebo/ BR
	N	Patients with event n (%)	N	Patients with event n (%)	RR[f,k] [95% CI] p value
Side effects[h]					
AE (presented additionally)	79	78 (98.7)	81	79 (97.5)	-
Severe AEs (grade ≥ 3)[l]	79	34 (43.0)	81	29 (35.8)	1.20 [0.82; 1.77]; 0.42
SAE	79	18 (22.8)	81	15 (18.5)	1.23 [0.67; 2.27]; 0.56
AE that led to discontinuation of study medication	79	4 (5.1)	81	5 (6.2)	0.82 [0.23; 2.94]; 1.00
Severe AE (grade ≥ 3) with incidence ≥ 5% according to SOC at week 120					
Metabolism and nutrition disorders	79	11 (13.9)	81	13 (16.0)	0.87 [0.41; 1.82]; p = 0.83
Elevated values in blood tests	79	7 (8.9)	81	3 (3.7)	2.39 [0.64; 8.92]; p = 0.21
Infections and infestations	79	8 (10.1)	81	4 (4.9)	2.05 [0.64; 6.54]; p = 0.24
Ear and labyrinth disorders	79	4 (5.1)	81	1 (1.2)	4.10 [0.47; 35.89]; p = 0.21
SAE with incidence ≥ 5% according to SOC at week 120					
Infections and infestations	79	6 (7.6)	81	4 (4.9)	1.54 [0.45; 5.24]; p = 0.53.
AEs with incidence ≥ 10% and statistically significant difference between the treatment arms by SOC and PT					
Diarrhoea (PT)	79	5 (6.3)	81	15 (18.5)	0.34 [0.13; 0.90]; 0.030
Tinnitus (PT)	79	3 (3.8)	81	11 (13.6)	0.28 [0.08; 0.96]; 0.047

a. Mortality was collected using safety.
b. Data cut-off: 16.10.2012 (addendum). Data from the final analysis, including data from the long-term observation of survival in subjects who discontinued the study.
c. The relative risk [95% CI] (calculated using the Cochrane-Mantel-Haenszel test, stratified by region (pooled centre) and caverns) for overall mortality is as follows: 2.61 [0.73; 9.28], p = 0.126.
d. Cox proportional hazards model stratified by region (pooled centre) and caverns.

e. The percentage of censored patients and the reasons for censoring were not presented in the study documents.
f. The percentage of missing values at week 120 (study discontinuation) was 36.7% in the intervention arm and 38.3% in the control arm.
g. The p value of the HR was calculated using a stratified log-rank test.
h. Final data cut-off: 31.01.2012.
i. Cochran-Mantel-Haenszel test stratified by region (pooled centre) and caverns.
j. According to the pharmaceutical company, missing values were imputed as non-responders.
k. Unstratified Cochran-Mantel-Haenszel test.
l. The study's own criteria were used for severity grading (DMID).
m. The base therapy was specified prior to randomisation and was standardised as far as possible. It consisted of the active ingredients kanamycin, ofloxacin, ethionamide, pyrazinamide and terizidone. In the event of reduced availability of the medicinal product or intolerance to one of the base therapy active ingredients administered, substitutions could be made.

Abbreviations used:
BR: base therapy; DMID: Division of Microbiology and Infectious Diseases; HR: hazard ratio; IQR: interquartile range; ITT: intention to treat population; CI: confidence interval; n.r.: not reached; PT: preferred term, RR: relative risk; SOC: MedRA system organ class; (S)AE: (serious) adverse event; WHO: World Health Organization.

Supplementary: STREAM study (stage 2): open-label phase III study comparing oral bedaquiline-containing treatment regimen[i] (arm C) vs control group [j] (arm B) - sub-population of patients with MDR-TB (defined as resistance to rifampicin and isoniazid); results at week 132 (database lock on 8 December 2022)

Mortality

STREAM study stage 2 (presented additionally) Endpoint	**Bedaquiline (arm C)[b]**		**Control (arm B)[b,c]**		**Bedaquiline vs control**
	N	Median time to event in months [95% CI] *Patients with event n (%)*	N	Median time to event in months [95% CI] *Patients with event n (%)*	HR[d,e] [95% CI] p value[f]
Mortality[a]					
Overall mortality	150	n.r. [n.r.; n.r.]; *7 (4.7)*	141	n.r. [n.r.; n.r.]; *4 (2.8)*	1.70 [0.50; 5.80]; 0.39

Morbidity

STREAM study stage 2 (presented additionally) Endpoint	Bedaquiline (arm C)[b]		Control (arm B)[b,c]		Bedaquiline vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR[f] [95% CI] p value[f]
Morbidity					
Cure (WHO 2008)[g]	150	120 (80.0)	141	91 (64.5)	1.24 [1.07; 1.44]; 0.004

Health-related quality of life

No data on the endpoint category of quality of life are available.

Side effects

STREAM study stage 2 (presented additionally) Endpoint	Bedaquiline (arm C)[b]		Control (arm B)[b,c]		Bedaquiline vs control
	N	Patients with event n (%)	N	Patients with event n (%)	RR[f] [95% CI] p value[f]
Side effects					
AE (presented additionally)	150	145 (96.7)	141	138 (97.9)	-
Severe AEs (grade ≥ 3)[g]	150	83 (55.3)	141	80 (56.7)	1.20 [0.82; 1.77]; 0.42
SAE	150	34 (22.7)	141	30 (21.3)	1.23 [0.67; 2.27]; 0.56
AE that led to discontinuation of study medication[h]	150	n.d.	141	n.d.	n.d.
Severe AE (grade ≥ 3) with incidence ≥ 5% according to SOC at week 132					
Investigations	150	64 (42.7)	141	57 (40.4)	1.05 [0.80; 1.39]; 0.70
Metabolism and nutrition disorders	150	14 (9.3)	141	9 (6.4)	1.46 [0.65; 3.27]; 0.36
Ear and labyrinth disorders	150	7 (4.7)	141	12 (8.5)	0.55 [0.22; 1.35]; 0.19

AEs with incidence ≥ 10% and statistically significant difference between the treatment arms by SOC and PT					
Gastritis (PT)	150	12 (8.0)	141	4 (2.8)	2.82 [0.93; 8.54]; 0.07
Nervous system disorders (SOC)	150	60 (40.0)	141	78 (55.3)	0.72 [0.57; 0.93]; 0.010
Fever (PT)	150	41 (27.3)	141	23 (16.3)	1.68 [1.06; 2.64]; 0.027
Ear and labyrinth disorders (SOC)	150	33 (22.0)	141	61 (43.3)	0.51 [0.36; 0.73]; < 0.001
Deafness (PT)	150	16 (10.7)	141	29 (20.6)	0.52 [0.29; 0.91]; 0.023
Tinnitus (PT)	150	6 (4.0)	141	25 (17.7)	0.23 [0.10; 0.53]; 0.001

a. According to information in Module 4 of the benefit dossier, the relative risk [95% CI] (unstratified) for overall mortality is: 1.62 [0.48; 5.41], p = 0.44.
b. In the control arm (arm B), protocol version 8.0 was used to switch the combination therapy from MFX to LFX. In the bedaquiline arm (arm C), LFX was administered over the entire treatment period.
c. As part of the salvage therapy, subjects in the control arm (arm B) could also receive bedaquiline for a maximum of 24 weeks during the 132-week observation period. A total of 29 subjects (14.4%; ITT population) in arm B received bedaquiline as part of salvage therapy. It is unclear how high the percentage is in the corresponding MDR-TB population.
d. Unstratified cox proportional hazards model.
e. The p value of the HR was calculated using an unstratified log-rank test.
f. Unstratified Cochran-Mantel-Haenszel test.
g. The study's own criteria were used for severity grading (DAIDS).
h. According to the pharmaceutical company in Module 4 of the benefit dossier, the results on AEs that led to therapy discontinuation were not presented because they are not comparable due to the non-standardised and incomplete survey.
i. Treatment regimen in arm B: Moxifloxacin (or levofloxacin protocol version 8.0 and higher) + clofazimine + ethambutol + pyrazinamide + isoniazid + prothionamide + kanamycin (or amikacin, depending on the national TB programme protocol version 8.0 and higher)
j. Treatment regimen in arm C: Bedaquiline + levofloxacin + clofazimine + ethambutol + pyrazinamide + isoniazid + prothionamide

Abbreviations used:
DAIDS: Division of AIDS; HR: hazard ratio; ITT: intention to treat; n.d.: no data available; CI: confidence interval; LFX: levofloxacin; MDR-TB: Multi-drug resistant tuberculosis; MFX: moxifloxacin; n.r.: not reached; PT: preferred term, RR: relative risk; SOC: MedRA system organ class; (S)AE: (serious) adverse event; WHO: World Health Organization.

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

Adult patients with pulmonary multidrug-resistant tuberculosis for whom an effective treatment regimen cannot be composed other than with bedaquiline (as part of an appropriate combination therapy) for reasons of resistance or intolerance

approx. 70 – 100 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: 12 December 2023):

https://www.ema.europa.eu/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 be used under *directly observed therapy* (DOT).

This medicinal product received a conditional marketing authorisation. 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.

4. Treatment costs

Annual treatment costs:

Adult patients with pulmonary multidrug-resistant tuberculosis for whom an effective treatment regimen cannot be composed other than with bedaquiline (as part of an appropriate combination therapy) for reasons of resistance or intolerance

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Bedaquiline	€ 29,739.44

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 January 2024)

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 Bedaquiline

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

Adult patients with pulmonary multidrug-resistant tuberculosis for whom an effective treatment regimen cannot be composed other than with bedaquiline (as part of an appropriate combination therapy) for reasons of resistance or intolerance

The following medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product in the therapeutic indication of the present resolution on the basis of the marketing authorisation under Medicinal Products Act are excluded from the designation, as the G-BA has identified at least considerable additional benefit for the combination with the assessed medicinal product in the present resolution:

delamanid (Deltyba)

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.