Resolution

Gemeinsamer Bundesausschuss

of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Resolution on the Benefit Assessment of Medicinal Products with New Active Ingredients in Accordance with Section 35a SGB V – Bedaquiline (Assessment of an Orphan Drug after Exceeding the Turnover Limit of €1 million)

of 4 July 2019

At its session on 4 July 2019 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: 4 July 2019
Entry into force on: 4 July 2019
Federal Gazette, BAnz. AT DD MM YYYY Bx

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 multi-drug-resistant tuberculosis [*multi-drug-resistant Mycobacterium tuberculosis* (MDR-TB)] in adult patients 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.

1. Extent of the additional benefit of the medicinal product

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. Pursuant 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). 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 multi-drug-resistant tuberculosis [*multi-drug-resistant Mycobacterium tuberculosis* (MDR-TB)], when an effective treatment regimen cannot be composed for reasons of resistance or tolerability other than with bedaquiline (as part of an appropriate combination regimen)

Extent of the additional benefit of bedaquiline as a component of appropriate combination regimen:

Considerable additional benefit

Study results according to endpoints:[1]

TMC207-C208 study: Phase II RCT comparing bedaquiline+background regimen (BR) vs. placebo+BR to week 120 (ITT population) - data cut-off 31 January 2012 (for morbidity and adverse events) and 16 October 2012 (for mortality)

[1] Data from the dossier evaluation by the G-BA (published on 15 April 2019) and from the amendment unless otherwise indicated.

C208 study Endpoint category Endpoint	Bedaquiline+BR		Placebo + BR		Bedaquiline+BR vs Placebo + BR	
	N	Patients with event n (%)	N	Patients with event n (%)	RR[a] [95% CI]; p value[b]	HR[c, d] [95% CI] p value[e]
Mortality						
Overall mortality[f]	79	10 (12.7)	81	3 (3.70)	2.61 [0.73; 9.28] p=0.1258	3.23 [0.85; 12.27] p=0.0855

C208 study Endpoint category Endpoint	Bedaquiline+BR		Placebo + BR		Bedaquiline+BR vs Placebo + BR
	N	Patients with event n (%)	N	Patients with event n (%)	RR[g] [95% CI]; p value[h]
Morbidity					
Cure	79	45 (57.0)	81	27 (33.3)	1.67 [1.17; 2.38] p = 0.0055
Relapse	79	6 (7.6)	81	11 (13.6)	0.56 [0.22; 1.44] p=0.2281

C208 study Endpoint category Endpoint	Bedaquiline+BR		Placebo + BR		Bedaquiline +BR vs Placebo + BR
	N	Median in days (IQR) [95% CI] Patients with event n (%)[i,j]	N	Median in days (IQR) [95% CI] Patients with event n (%)[i,j]	HR[k,l] [95% CI] p value[m]
Absence of pathogens in sputum	79	86 [70; 112] *48 (60.8)*	81	345 [140; n.a.] *37 (35.7)*	2.01 1.29; 3.14]). p=0.0020

C208 study Endpoint category Endpoint	Bedaquiline+BR		Placebo + BR		Bedaquiline+BR vs Placebo + BR
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p value
Quality of life					
No data collected					

C208 study Endpoint category Endpoint	Bedaquiline+BR		Placebo + BR		Bedaquiline+BR vs Placebo + BR
	N	Patients with event n (%)	N	Patients with event n (%)	RR[g] [95% CI]; p value[h]
Side effects					
AEs					
AEs up to week 24	79	77 (97.5)	81	77 (95.1)	1.03 [0.96; 1.09] p = 0.6816
AEs up to week 120	79	78 (98.7)	81	79 (97.5)	1.01 [0.97; 1.06] p=1.0000
AEs with a severity grade of ≥ 3					
AEs up to week 24	79	22 (27.8)	81	19 (23.5)	1.19 [0.7; 2.02] p = 0.5887
AEs up to week 120	79	34 (43.0)	81	29 (35.8)	1.20 [0.82; 1.77] p = 0.4188
SAEs					
SAEs up to week 24	79	6 (7.6)	81	1 (1.2)	6.15 [0.76; 49.95] p = 0.0620
SAEs up to week 120	79	18 (22.8)	81	15 (18.5)	1.23 [0.67; 2.27] p = 0.5607
AE that led to discontinuation of the trial drug					
Discontinuation due to AEs up to week 24	79	4 (5.1)	81	5 (6.2)	0.82 [0.23; 2.94] p=1.0000
Discontinuation due to AEs up to week 120	79	4 (5.1)	81	5 (6.2)	0.82 [0.23; 2.94] p=1.0000
Death[f]					
Discontinuation due to AEs up to week 24	79	1 (1.3)	81	0 (0)	n.ev.

C208 study Endpoint category Endpoint	Bedaquiline+BR		Placebo + BR		Bedaquiline+BR vs Placebo + BR
	N	Patients with event n (%)	N	Patients with event n (%)	RR[g] [95% CI]; p value[h]
Discontinuation due to AEs up to week 120	79	10 (12.7)	81	3 (3.7)	2.61 [0.73; 9.28] p=0.1258

C208 study MedDRA System Organ Class Preferred Term	Bedaquiline+BR		Placebo + BR		Bedaquiline+BR vs Placebo + BR
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
AEs with an incidence of ≥ 10% in one of the study arms and at PT level with a difference of at least 10% between the study arms up to week 120					
Gastrointestinal disorders	79	53 (67.1)	81	53 (65.4)	1.03 [0.82; 1.28] p=0.8682
Diarrhoea	79	5 (6.3)	81	15 (18.5)	0.34 [0.13; 0.90]; p=0.0297
Dyspepsia	79	4 (5.1)	81	12 (14.8)	0.34 [0.12; 1.01]; p=0.0627).
Infections and infestations	79	41 (51.9)	81	44 (54.3)	0.96 [0.71; 1.28]; p=0.8742
Nervous system disorders	79	40 (50.6)	81	33 (40.7)	1.24 [0.88; 1.75]; p=0.2665
Musculoskeletal and connective tissue disorders	79	39 (49.4)	81	40 (49.4)	1.00 [0.73; 1.37]; p=1.0000
Arthralgia	79	29 (36.7)	81	18 (22.9)	1.35 [0.85; 2.14]; p=0.2357
Metabolism and nutrition disorders	79	35 (44.3)	81	35 (43.2)	1.03 [0.72; 1.46]; p=1.0000
General disorders and administration site conditions	79	31 (39.2)	81	27 (33.3)	1.18 [0.78; 1.78]; p=0.5112
Respiratory, thoracic and mediastinal disorders	79	31 (39.2)	81	35 (43.2)	0.91 [0.63; 1.32]; p=0.6331
Ear and labyrinth disorders	79	27 (34.2)	81	29 (35.8)	0.95 [0.63; 1.46]; p=0.8693
Tinnitus	79	3 (3.8)	81	11 (13.6)	0.28 [0.08; 0.96]; p=0.0471

C208 study MedDRA System Organ Class Preferred Term	Bedaquiline+BR		Placebo + BR		Bedaquiline+BR vs Placebo + BR
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
Skin and subcutaneous tissue disorders	79	25 (31.6)	81	28 (34.6)	0.92 [0.59; 1.42]; p=0.7387
Investigations	79	23 (29.1)	81	24 (29.6)	0.98 [0.61; 1.59]; p=1.0000
Eye disorders	79	18 (22.8)	81	20 (24.7)	0.92 [0.53; 1.61]; p=0.8534
Psychiatric disorders	79	18 (22.8)	81	17 (21.0)	1.09 [0.60; 1.95]; p=0.8494
Insomnia	79	13 (16.5)	81	10 (12.3)	1.33 [0.62; 2.86] p=0.5050
Injury, poisoning and procedural complications	79	11 (13.9)	81	15 (18.5)	0.75 [0.37; 1.53] p=0.5219
Reproductive system and breast disorders	79	11 (13.9)	81	15 (18.5)	0.75 [0.37; 1.53] p=0.5219
Blood and lymphatic system disorders	79	10 (12.7)	81	7 (8.6)	1.46 [0.59; 3.66] p=0.4513
Cardiac disorders	79	6 (7.6)	81	13 (16.0)	0.47 [0.19; 1.18] p=0.1417

C208 study MedDRA System Organ Class[v] Preferred Term	Bedaquiline+BR		Placebo + BR		Bedaquiline+BR vs Placebo + BR
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][x] p value
Serious AEs (grade ≥3) with an incidence of ≥ 5 % in one of the study arms up to week 120					
AEs with a severity grade of ≥ 3	79	34 (43.0)	81	29 (35.8)	1.20 [0.82; 1.77]; p=0.4188
Metabolism and nutrition disorders	79	11 (13.9)	81	13 (16.0)	0.87 [0.41; 1.82]; p=0.8256
Hyperuricaemia	79	10 (12.7)	81	13 (16.0)	0.79 [0.37; 1.69]; p=0.6537
Elevated blood test values	79	7 (8.9)	81	3 (3.7)	2.39 [0.64; 8.92]; p=0.2074
Infections and infestations	79	8 (10.1)	81	4 (4.9)	2.05 [0.64; 6.54]; p=0.2438

C208 study MedDRA System Organ Class[v] Preferred Term	Bedaquiline+BR		Placebo + BR		Bedaquiline+BR vs Placebo + BR
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI][x] p value
Ear and labyrinth disorders	79	4 (5.1)	81	1 (1.2)	4.10 [0.47; 35.89]; p=0.2071

C208 study MedDRA System Organ Class Preferred Term	Bedaquiline+BR		Placebo + BR		Bedaquiline+BR vs Placebo + BR
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value
SAEs with an incidence of ≥ 5 % in one of the study arms up to week 120					
SAEs	79	18 (22.8)	81	15 (18.5)	1.23 [0.67; 2.27]; p=0.5607
Infections and infestations	79	6 (7.6)	81	4 (4.9)	1.54 [0.45; 5.24]; p=0.5316

a: Mantel-Haenszel method
b: Cochran-Mantel Haenszel chi-squared test stratified by region (pooled centre) and infected cavities
c: Stratified Cox regression with treatment, pooled centre and infected cavities as covariates
d: The proportion of censored patients and the reasons for censoring were not presented in the study documents.
e: The HR p value was calculated by means of a Wald test.
f: Data from the final analysis, including data from the long-term observation of survival in study withdrawal subjects
g: Mantel-Haenszel estimator stratified by region (pooled centre) and infected cavities
h: p value based on Cochran-Mantel-Haenszel chi-squared test
i: Patients whose sputum was free of pathogens (the first of 2 consecutive samples) during the study or at the last observed visit during the analysis period were censored at the upper limit of the investigated time window.
j: Patients who withdrew prematurely from the study before the end of the analysis period were classified as "sputum not free of pathogens" (primary missing = failure analysis), and their time to pathogen-free sputum was censored at the time of the last sputum evaluation, regardless of whether the patient had "sputum free of pathogens" at the end of the study or not.
k: Hazard Ratio (based on a Cox proportional-hazards model stratified for treatment, region (pooled centre) and infected cavities)
l: The proportion of censored patients and the reasons for censoring were not presented in the study documents.
m: The HR p value was calculated by means of a Wald test.

Abbreviations: BR: background regimen; HR: hazard ratio; ITT: intention-to-treat population; IQR: inter-quartile range; CI confidence interval; N number of patients; n: number of patients observed; n.a.: not achieved; n.ev.: not evaluable; RR: relative risk; AE: adverse event; SAE: serious adverse event.

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

Adult patients with pulmonary multi-drug-resistant tuberculosis [*multi-drug-resistant Mycobacterium tuberculosis* (MDR-TB)], when an effective treatment regimen cannot be composed for reasons of resistance or tolerability other than with bedaquiline (as part of an appropriate combination regimen)

Approx. 70–100 patients

3. Requirements for a quality-assured application

The requirements of 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 April 2019):
https://www.ema.europa.eu/documents/product-information/sirturo-epar-product-information_en.pdf

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

It is recommended to administer bedaquiline (Sirturo) under *directly observed therapy* (DOT).

This medicinal product was authorised under "specific 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.

4. Treatment costs

Annual treatment costs:

Adult patients with pulmonary multi-drug-resistant tuberculosis [*multi-drug-resistant Mycobacterium tuberculosis* (MDR-TB)], when an effective treatment regimen cannot be composed for reasons of resistance or tolerability other than with bedaquiline (as part of an appropriate combination regimen)

Designation of the therapy	Annual treatment costs/patient
Bedaquiline	€32,735.84

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 June 2019)

Costs for additionally required SHI services: not applicable

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 4 July 2019.

2. The period of validity of the resolution is limited to 30 June 2021.

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

Berlin, 4 July 2019

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

Prof Hecken