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
Delamanid (repeal of the exemption: pulmonary multi-drug resistant tuberculosis, ≥ 10 kg)

of 5 May 2022

At its session on 5 May 2022, 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 D 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 Delamanid as follows:

Courtesy translation – only the German version is legally binding.

Delamanid

Resolution of: 5 May 2022
Entry into force on: 5 May 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 16 September 2021):

Deltyba is indicated for use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, adolescents, children and infants with a body weight of at least 10 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.

Therapeutic indication of the resolution (resolution of 5 May 2022):

See therapeutic indication according to marketing authorisation.

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

Delamanid 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).

a) Adults with pulmonary multi-drug resistant tuberculosis when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability

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

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

b) Children and adolescents with pulmonary multi-drug resistant tuberculosis and a body weight of at least 10 kg, when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability

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

Courtesy translation – only the German version is legally binding.

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Study results according to endpoints:[1]

a) Adults with pulmonary multi-drug resistant tuberculosis when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability

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	↔	No relevant differences for the benefit assessment.
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 ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

[1] Data from the dossier assessment of the G-BA (published on 15. Februar 2022), unless otherwise indicated.

Courtesy translation – only the German version is legally binding.

RCT 213: Delamanid plus OBR vs placebo plus OBR, 130 weeks (ITT population)

Mortality

Study 213 Endpoint	**Delamanid plus OBR**		**Placebo plus OBR**		**Intervention vs control**
	N	*Deaths n (%)*	N	*Deaths n (%)*	Relative risk of death [95% CI]; p value[a]
Overall mortality	341	18 (5.3)	170	8 (4.7)	1.12 [0.50; 2.53]; 0.7815

Morbidity

Study 213 Endpoint	**Delamanid plus OBR**		**Placebo plus OBR**		**Intervention vs control**
	N	*Patients with event n (%)*	N	*Patients with event n (%)*	Relative Risk [95% CI]; p value[a]
Cure	339	264 (77.9)	170	130 (76.5)	1.02 [0.92; 1.13]; 0.7209
Permanent sputum culture conversion (presented additionally)					
Subjects with permanent sputum culture conversion	341	263 (77.1)	170	132 (77.6)	
	N	Median in days (SCC) [95% CI]	N	Median in days [95% CI]	Hazard ratio [95% CI]; p value[b]
Median time to permanent SCC	341	48 [42; 56]	170	56 [50; 64]	1.09 [0.88; 1.34]; 0.4358

Courtesy translation – only the German version is legally binding.

Study 213 Endpoint	Delamanid plus OBR			Placebo plus OBR		
	Screening N = 341	Week 26 N = 307	Month 18 N = 287	Screening N = 170 .	Week 26 N = 154	Month 18 N = 146
	n (%)[c]	*n (%)*[c]	*n (%)*[c]	*n (%)*[c]	*n (%)*[c]	*n (%)*[c]
Clinical signs and symptoms						
Chest pain						
Symptom present	139 (40.8)	28 (9.1)	16 (5.6)	83 (48.8)	14 (9.1)	11 (7.5)
Frequency						
sometimes	102 (29.9)	27 (8.8)	16 (5.6)	56 (32.9)	11 (7.1)	9 (6.2)
often	29 (8.5)	1 (0.3)	0	19 (11.2)	3 (1.9)	2 (1.4)
always	8 (2.3)	0	0	8 (4.7)	0	0
Intensity						
mild	99 (29.0)	28 (9.1)	16 (5.6)	62 (36.5)	10 (6.5)	26 (6.0)
moderate	40 (11.7)	0	0	21 (12.4)	4 (2.6)	1 (0.2)
severe	0	0	0	0	0	0
Cough						
Symptom present	315 (92.4)	123 (40.1)	57 (19.9)	161 (94.7)	51 (33.1)	35 (24.0)
Frequency						
sometimes	140 (41.1)	118 (38.4)	53 (18.5)	66 (38.8)	46 (29.9)	29 (19.9)
often	118 (34.6)	3 (1.0)	2 (0.7)	71 (41.8)	4 (2.6)	3 (2.1)
always	57 (16.7)	2 (0.7)	2 (0.7)	24 (14.1)	1 (0.6)	3 (2.1)
Intensity						
mild	163 (47.8)	118 (38.4)	54 (18.8)	88 (51.8)	45 (29.2)	28 (19.2)
moderate	145 (42.5)	5 (1.6)	3 (1.0)	70 (41.2)	6 (3.9)	7 (4.8)
severe	7 (2.1)	0	0	3 (1.8)	0	0
Dyspnoea						
Symptom present	164 (48.1)	44 (14.3)	28 (9.8)	79 (46.5)	18 (11.8)	18 (12.3)
Frequency						
sometimes	101 (29.6)	39 (12.7)	23 (8.0)	50 (29.4)	13 (8.5)	12 (8.2)
often	46 (13.5)	4 (1.3)	5 (1.7)	20 (11.8)	2 (1.3)	4 (2.7)
always	17 (5.0)	1 (0.3)	0	9 (5.3)	3 (2.0)	2 (1.4)
Intensity						
mild	115 (33.7)	39 (12.7)	24 (8.4)	56 (32.9)	14 (9.2)	13 (8.9)
moderate	48 (14.1)	5 (1.6)	3 (1.0)	22 (12.9)	3 (2.0)	5 (3.5)
severe	1 (0.3)	0	1 (0.3)	1 (0.6)	1 (0.7)	0
Feverish feeling						
Symptom present	102 (29.9)	5 (1.6)	2 (0.7)	48 (28.2)	4 (2.6)	2 (1.4)

Courtesy translation – only the German version is legally binding.

Study 213 Endpoint	Delamanid plus OBR			Placebo plus OBR		
	Screening N = 341	Week 26 N = 307	Month 18 N = 287	Screening N = 170 .	Week 26 N = 154	Month 18 N = 146
	n (%)[c]	*n (%)*[c]	*n (%)*[c]	*n (%)*[c]	*n (%)*[c]	*n (%)*[c]
Frequency						
sometimes	68 (19.9)	5 (1.6)	2 (0.7)	31 (18.2)	4 (2.6)	2 (1.4)
often	23 (6.7)	0	0	12 (7.1)	0	0
always	11 (3.2)	0	0	5 (2.9)	0	0
Intensity						
mild	68 (19.9)	3 (1.0)	2 (0.7)	29 (17.1)	3 (1.9)	2 (1.4)
moderate	33 (9.7)	2 (0.7)	0	19 (11.2)	1 (0.6)	0
severe	1 (0.3)	0	0	0	0	0
Haemoptysis						
Symptom present	93 (27.3)	5 (1.6)	1 (0.3)	44 (25.9)	4 (2.6)	0
Frequency						
sometimes	80 (23.5)	3 (1.0)	1 (0.3)	37 (21.8)	4 (2.6)	0
often	9 (2.6)	2 (0.7)	0	7 (4.1)	0	0
always	4 (1.2)	0	0	0	0	0
Intensity						
mild	75 (22.0)	5 (1.6)	1 (0.3)	37 (21.8)	4 (2.6)	0
moderate	17 (5.0)	0	0	6 (3.5)	0	0
severe	1 (0.3)	0	0	1 (0.6)	0	0
Appetite loss						
Symptom present	111 (32.6)	13 (4.2)	6 (2.1)	64 (37.6)	8 (5.2)	3 (2.1)
Frequency						
sometimes	48 (14.1)	9 (2.9)	5 (1.7)	27 (15.9)	7 (4.5)	2 (1.4)
often	33 (9.7)	4 (1.3)	1 (0.3)	17 (10.0)	1 (0.6)	1 (0.7)
always	30 (8.8)	0	0	19 (11.2)	0	0
Intensity						
mild	61 (17.9)	10 (3.3)	5 (1.7)	39 (22.9)	7 (4.5)	2 (1.4)
moderate	49 (14.4)	3 (1.0)	1 (0.3)	24 (14.1)	1 (0.6)	1 (0.7)
severe	1 (0.3)	0	0	1 (0.6)	0	0
Night sweats						
Symptom present	134 (39.3)	9 (2.9)	6 (2.1)	63 (37.1)	3 (1.9)	0
Frequency,						
sometimes	76 (22.3)	8 (2.6)	6 (2.1)	29 (17.1)	3 (1.9)	0
often	41 (12.0)	1 (0.3)	0	25 (14.7)	0	0
always	17 (5.0)	0	0	9 (5.3)	0	0
Intensity,						
mild						
moderate	81 (23.8)	8 (2.6)	6 (2.1)	31 (18.2)	3 (1.9)	0

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Study 213 Endpoint	Delamanid plus OBR			Placebo plus OBR		
	Screening N = 341	Week 26 N = 307	Month 18 N = 287	Screening N = 170 .	Week 26 N = 154	Month 18 N = 146
	n (%)[c]	*n (%)*[c]	*n (%)*[c]	*n (%)*[c]	*n (%)*[c]	*n (%)*[c]
severe	50 (14.7) 3 (0.9)	1 (0.3) 0	0 0	28 (16.5) 4 (2.4)	0 0	0 0

Health-related quality of life

Study 213 Endpoint	Delamanid plus OBR	Placebo plus OBR	Intervention vs control
Health-related quality of life			
Study 213	not assessed		

Side effects

Study 213 Endpoint	Delamanid plus OBR		Placebo plus OBR		Intervention vs control
	N[d]	*n (%)*	N[d]	*n (%)*	Relative risk [95% CI] p value)[a]
AE[e]	341	336 (98.5)	170	165 (97.1)	-
Severe AEs[e] (presented additionally)	341	81 (23.8)	170	37 (21.8)	1.09 [0.78; 1.54]; 0.6155
Serious AEs[e]	341	89 (26.1)	170	47 (27.6)	0.94 [0.70; 1.28]; 0.7095
AEs that led to discontinuation of delamanid or placebo	341	8 (2.3)	170	3 (1.8)	1.33 [0.36; 4.95]; 0.6699

Study 213 Endpoint ***MedDRA system organ class*** *Preferred term*	Delamanid plus OBR		Placebo plus OBR	
	N	***n (%)***	**N**	***n (%)***
AEs[e] of any severity with an incidence of ≥ 10% in one of the study arms and a difference of ≥ 5% between the treatment groups				
Pain in the upper abdomen	341	35 (10.3)	170	28 (16.5)

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Study 213 **Endpoint** ***MedDRA system organ class*** *Preferred term*	**Delamanid plus OBR**		**Placebo plus OBR**	
	N	***n (%)***	**N**	***n (%)***
Gastritis	341	77 (22.6)	170	27 (15.9)
Nausea	341	95 (27.9)	170	56 (32.9)
Back pain	341	44 (12.9)	170	31 (18.2)
Nervous system disorders	341	**191 (56.0)**	170	**80 (47.1)**
Headache	341	104 (30.5)	170	39 (22.9)
Psychiatric disorders	341	**147 (43.1)**	170	**92 (54.1)**

a) p value based on Cochran-Mantel-Haenszel test. No data available on stratification variables.
b) Analysis stratified by risk category based on a Cox model; p value based on Wald test.
c) Percentages refer to the subjects with available values.
d) Safety population
e) AEs include events that occurred after the first dose of study medication and events that persisted from baseline and deteriorated, were serious, were related to the medicinal product, or resulted in death or discontinuation, interruption or reduction of the medicinal product

Abbreviations:

CI = confidence interval; MedDRA:: Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with event; OBR = Optimised Background Treatment Regimen; SAE = serious adverse event; AE = adverse event;

b) <u>Children and adolescents with pulmonary multi-drug resistant tuberculosis and a body weight of at least 10 kg, when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability</u>

Summary of results for relevant clinical endpoints

Endpoint category	**Direction of effect/ risk of bias**	**Summary**
Mortality	n.a.	There are no assessable data.
Morbidity	n.a.	There are no assessable data.
Health-related quality of life	∅	No data available.
Side effects	n.a.	There are no assessable data.
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data		

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↓: 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

Study 233 (single-arm, open-label): Delamanid plus OBR; age group 3 to 5-year-old children; 24 months

Mortality

Study 233 Endpoint	**Delamanid plus OBR**	
	N[a]	*Deaths n*
Overall mortality	12	1

Morbidity

Study 233 Endpoint	**Delamanid plus OBR**	
	N	*Patients with event n (%)*
Cure	12	3 (25)

Study 233 Endpoint	**Delamanid plus OBR**					
		Baseline[b]		Day 182		Day 365
	N[a]	*n (%)*	N	*n (%)*	N	*n (%)*
Clinical signs and symptoms						
Cough	12	1 (8)	12	0	11	0
Fever	12	0	12	0	11	0
Weight loss	12	1 (8)	12	0	11	0
Failure to thrive	12	0	12	0	11	0
Haemoptysis	12	0	12	0	11	0
Dyspnoea	12	0	12	0	11	1 (8)
Thoracic/chest pain	12	0	12	0	11	0
Night sweats	12	0	12	1 (8)	11	0
Appetite loss	12	1 (8)	12	1 (8)	11	0

Courtesy translation – only the German version is legally binding.

Health-related quality of life

Study 233 Endpoint	Delamanid plus OBR
Quality of life	
Study 233	Not assessed

Side effects

Study 233 Endpoint	Delamanid plus OBR	
	N[a]	*n (%)*
AE[c]	12	12 (100)
Severe AEs	12	1 (8)
SAE	12	2 (17)
AEs which led to the discontinuation of the study medication	12	0

Study 233 **Endpoint** ***MedDRA system organ class*** *Preferred term*	**Delamanid plus OBR**	
	N[a)]	***n (%)***
AEs[d] of any severity with incidence ≥ 10%		
Endocrine disorders	**12**	**2 (17)**
Hypothyroidism	12	2 (17)
Gastrointestinal disorders	**12**	**5 (42)**
Vomiting	12	2 (17)
General disorders and administration site conditions	**12**	**2 (17)**
Fever	12	2 (17)
Infections and infestations	**12**	**11 (92)**
Lower respiratory tract infection	12	3 (25)
Pneumonia	12	3 (25)
Upper respiratory tract infection	12	5 (42)
Injury, poisoning and procedural complications	**12**	**4 (33)**
Skin tear	12	2 (17)
Investigations	**12**	**4 (33)**
Elevated corticotropin level in the blood	12	2 (17)

Courtesy translation – only the German version is legally binding.

Study 233 **Endpoint** ***MedDRA system organ class*** *Preferred term*	**Delamanid plus OBR**	
	N[a)]	***n (%)***
Liver function test elevated levels	12	2 (17)
Metabolism and nutrition disorders	**12**	**4 (33)**
Hyperuricaemia	12	4 (33)
Musculoskeletal and connective tissue disorders	**12**	**4 (33)**
Arthralgia	12	3 (25)
Nervous system disorders	**12**	**4 (33)**
Headache	12	2 (17)
Respiratory, thoracic and mediastinal disorders	**12**	**2 (17)**
Skin and subcutaneous tissue disorders	**12**	**2 (17)**

a) Safety population
b) Baseline is defined as the last assessment prior to the study medication delamanid.
c) Patient relevance of the overall category unclear
d) AEs that began after the start of treatment with the study medication or if the AE was already present at baseline and was severe, was related to the study medication, or resulted in death or discontinuation, interruption or reduction of the study medication. Subjects were counted only for the most severe of several of a given AE as determined by MedDRA.

Abbreviations:
CI = confidence interval; MedDRA:: Medical Dictionary for Regulatory Activities; N = number of patients evaluated; n = number of patients with event, OBR = Optimised Background Treatment Regimen; SAE = serious adverse event; AE = adverse event; TEAE = treatment-emergentadverse event.

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

a) <u>Adults with pulmonary multi-drug resistant tuberculosis when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability</u>

approx. 70 - 100 patients

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b) Children and adolescents with pulmonary multi-drug resistant tuberculosis and a body weight of at least 10 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability

approx. 10 - 14 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 Deltyba (active ingredient: delamanid) at the following publicly accessible link (last access: 21 January 2022):

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

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

Use of delamanid as directly observed therapy (DOT) is recommended.

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.

4. Treatment costs

Annual treatment costs:

a) Adults with pulmonary multi-drug resistant tuberculosis (MDR-TB) when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Delamanid	€ 23,748.34

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2022)

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b) Children and adolescents with pulmonary multi-drug resistant tuberculosis (MDR-TB) and a body weight of at least 10 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Delamanid FCT	€ 11,874.17 - € 23,748.34
Delamanid TOS[2]	incalculable

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 April 2022)

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 5 May 2022.

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

Berlin, 5 May 2022

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

Prof. Hecken

[2] Delamanid 25 mg, tablets for oral suspension (TOS), are currently not available on the German market. Therefore, cost representation is not possible

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