Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) 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

Contents

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V). Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 50 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, subsection 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the marketing authorisation studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a, paragraph 1, sentence 12 SGB V). According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be

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completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient delamanid was listed for the first time on 1 June 2014 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

The pharmaceutical company submitted an application for exemption from the obligation to submit evidence pursuant to Section 4 VerfO before placing the product on the market. By resolution of 17 April 2014, the pharmaceutical company was exempted from the obligation to submit evidence according to Chapter 5, Section 5 of the Rules of Procedure (VerfO) of the Federal Joint Committee and the proprietary medicinal product concerned was exempted from the benefit assessment according to the provisions of Chapter 5 VerfO.

On 27 October 2020, delamanid received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

Upon extension of the therapeutic indication, the pharmaceutical company was informed by the G-BA that the G-BA would take this fact as an opportunity to review the continued exemption of the medicinal product on the basis of Chapter 5, Section 15 VerfO. In a letter dated 22 October 2020, the pharmaceutical company submitted a complete application for exemption pursuant to Chapter 5, Section 15, paragraph 1, sentences 2 to 4 VerfO for the entire proprietary medicinal product Deltyba® for all therapeutic indications, including the new therapeutic indication. The application for exemption from the benefit assessment due to minor importance pursuant to Section 35a, paragraph 1a SGB V for the medicinal product Deltyba® was not granted, taking into account the documents submitted, and the decision on the exemption of the medicinal product Deltyba® from the benefit assessment due to insignificance pursuant to Section 35a, paragraph 1a SGB V of 17 April 2014 was repealed with effect from 17 December 2020.

With the repeal of the decision of exemption, the assessment procedure according to Section 35a SGB V for the entire proprietary medicinal product Deltyba® for all approved therapeutic indications would have started on 17 December 2020, however, the pharmaceutical company had also submitted an application for exemption from the obligation to submit evidence according to Section 35a paragraph 1, sentence 3, numbers 2 and 3 SGB V due to reserve status according to Section 35a, paragraph 1c SGB V in a letter dated 22 October 2020. The application procedure was also suspended by resolution of 17 December 2020. This resulted in the temporary suspension of the obligation to transmit the dossier according to Chapter 5, Section 11 VerfO. The suspension ended three months after the G-BA's Rules of Procedure (VerfO), adapted on the basis of Section 35a, paragraph 1c, sentence 4 SGB V, took effect, and after publication of the criteria - determined by the Robert Koch Institute (RKI) in agreement

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with the Federal Institute for Drugs and Medical Devices (BfArM) - for classification as a reserve antibiotic according to Section 35a, paragraph 1c, sentence 5 SGB V. The pharmaceutical company was obliged to submit the grounds for the application in accordance with the adapted regulations in the VerfO on the basis of the criteria of the RKI pursuant to Section 35a, paragraph 1c, sentence 5 SGB V at the latest by the date on which the suspension ends. Otherwise, the application was considered withdrawn. In the event that no application justification was submitted by the date of expiry of the suspension, restoration to the previous status was granted with regard to the submission of the application with effect from the time of the first obligation to submit evidence pursuant to Section 35a, paragraph 1, sentence 3 SGB V.

In a letter dated 3 August 2021, the pharmaceutical company was informed that with the entry into force of the adapted Rules of Procedure on 3 August 2021, there is an obligation to submit both a confirmation of the application pursuant to Section 35a, paragraph 1c SGB V and an application justification in accordance with the adapted regulations in Chapter 5, Section 15a, paragraph 2 VerfO. The pharmaceutical company was informed that both the confirmation of the application and the further application justification for a procedure according to Section 35a paragraph 1c SGB V must also include the new therapeutic indication of Deltyba®, which had received a "Positive Opinion" from the EMA on 22 July 2021. In the event that no confirmation of the application was submitted by the date of expiry of the suspension, or no further justification was submitted by 31 December 2021 at the latest, the application for exemption pursuant to Section 35a paragraph 1c SGB V was deemed to be withdrawn. The attention of the pharmaceutical company was drawn to the obligation to submit a dossier according to Chapter 5, Section 11 VerfO (taking into account all approved therapeutic indications) at the latest by the date of expiry of the suspension, i.e. on 3 November 2021, if no confirmation of the application is submitted.

On 16 September 2021, delamanid received marketing authorisation for another new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 3 November 2021, i.e. by the date of expiry of the suspension of the procedure, the pharmaceutical company submitted the final dossier to the G-BA and withdrew the application for exemption from the obligation to submit evidence according to Section 35a, paragraph 1, sentence 3, numbers 2 and 3 SGB V due to reserve status according to Section 35a, paragraph 1c SGB V.

Delamanid for the treatment of pulmonary multi-drug resistant tuberculosis is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment

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costs and patient numbers. The benefit assessment was published on 15 February 2022 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G21-34) prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of delamanid.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Delamanid (Deltyba) in accordance with the product information

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 the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of delamanid is assessed as follows:

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

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

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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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

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

Justification:

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

The marketing authorisation of delamanid in the therapeutic indication of adult patients with MDR-TB was granted as a conditional marketing authorisation on 27 April 2014 on the basis of the pivotal study 242-07-204 (= study 204). A requirement of the EMA for the conditional marketing authorisation was the completion of the confirmatory phase III study 242-09-213 (= study 213) and the submission of the study results.

Study 204 is a phase II, multicentre, double-blind, randomised placebo-controlled study to evaluate the safety, efficacy and pharmacokinetics of delamanid in combination with optimised standard combination regimen (OBR: Optimised Background Regimen) versus placebo plus OBR in pulmonary sputum culture-positive MDR-TB. In this phase II study, treatment was with delamanid (100 mg BID or 200 mg BID) for 8 weeks. The treatment duration of 24 weeks, which is in line with the product information, was thus not reached in the study 204. With the EMA-commissioned study 213, data are available for the controlled comparison of delamanid versus placebo over 26 weeks. Study 213 represents the higher-quality evidence on the use of delamanid in line with the product information compared with study 204 and is used for the benefit assessment.

The multicentre, randomised, double-blind phase III study 213 investigated the safety and efficacy of oral delamanid versus placebo, each in combination with OBR, in adult patients with pulmonary sputum culture-positive MDR. The OBR was carried out according to the WHO guidelines for the treatment of resistant tuberculosis and national treatment standards valid at the time. The patients in study 213 were not offered treatment with bedaquiline in the comparator arm, as the active ingredient was only approved for the first time in March 2014 during the ongoing study and the clinical significance could not yet be conclusively assessed at that time.

In the parallel-group study that lasted a total of 130 weeks, the adult patients were treated with delamanid or placebo for 6 months in combination with OBR. Treatment with OBR was then continued for 12 to 18 months; follow-up was until week 130. In the study, patients were randomised to the two study arms delamanid plus OBR (N=341) or placebo plus OBR (N=170) in a 2:1 ratio. At baseline, no evidence of MDR-TB could be provided by means of liquid culture for a not so insignificant percentage of the study participants: 34% in the delamanid arm and 41% in the placebo arm. However, an MDR-TB diagnosis based on a sputum sample taken up to 60 or 90 days before the start of screening, depending on the study protocol version, was part of the inclusion criteria of the studies. In the process, an MDR-TB diagnosis either requires the presence of a TB-positive culture with documented resistance to isoniazid and rifampicin or a positive sputum smear for acid-fast bacteria or a positive rapid TB test together with a

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positive rapid test for resistance to rifampicin alone or to rifampicin and isoniazid. Nevertheless, uncertainties remain, which is why the evidence at baseline could not be provided for a decisive percentage of the study participants.

For the benefit assessment, the final analysis of study 213 with data cut-off of 04.07.2016 is used for the categories of mortality, morbidity and side effects. No subgroup analyses were submitted as part of the benefit assessment.

The pharmaceutical company also presented the results of studies 208, 116 and 401 in the dossier. In the multicentre, uncontrolled, open-label follow-up study 208, patients could receive delamanid (100mg BID or 200 mg BID) + OBR for up to 6 additional months beyond the exposure in the study 204. Study 116 contains follow-up data from patients who received treatment with delamanid as part of a study. Study 401 assessed the endpoints of sputum culture conversion and safety and tolerability of patients in the compassionate use programme. Studies 208, 116 and 401 are not presented in the benefit assessment due to the very low significance of uncontrolled data in the presence of an RCT.

Mortality

Overall survival

Overall mortality was recorded in the study 213. By week 130, 18 deaths occurred in the delamanid arm (5.3%) and 8 deaths in the placebo arm (4.7%); the result is not statistically significant.

Morbidity

Sustained sputum culture conversion

Sustained sputum culture conversion (SCC) is defined as SCC achieved by month 6 and not followed by a confirmed positive result (≥ 2 positive findings) (two consecutive sputum samples, which were obtained at least 25 days apart and were *M. tuberculosis negative* using the MGIT culture system). The status in relation to sustained SCC should be determined at months 18, 24 and 30 respectively. For sustained SCC, a subject should have negative culture results at least at two time points after the 6-month treatment period up to month M (M = 18, 24 and 30). A time-to-event analysis ("time to sustained SCC") was also provided.

The operationalisation of the endpoint in the study thus required that evidence of sustained sputum culture conversion was provided by having negative culture results at a minimum of 2 additional time points in addition to the initial 2 samples (at a minimum interval of 25 days). In the German S2k guideline for the treatment of tuberculosis sensitive to medication (currently in revision), three negative microscopic sputum samples are recommended before isolation is lifted.

The absence of pathogens is a basic prerequisite for lifting isolation because the risk of infection no longer exists. The length of time patients is isolated has an impact on quality of life and is patient-relevant. However, the pharmaceutical company did not collect data on quality of life, hospitalisation or isolation. The duration of isolation depends on other factors

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in addition to the absence of pathogens. It is therefore questionable to what extent the endpoint "time to sustained SCC" alone can provide information on the actual duration of patient isolation in the present operationalisation. It should also be taken into account that there are overlaps with regard to the operationalisation for "sustained SCC" with the endpoint "cure" presented. The results of the endpoint are therefore only presented additionally. In the present study, sustained sputum culture conversion was evaluated by number of events and as time-to-event analysis. Both evaluations show no significant differences between the study arms.

Cure

The endpoint "cure" was operationalised as a secondary endpoint largely using the WHO 2008 definition of cure. According to the WHO 2008, a cure of the affected person is achieved when the treatment has been terminated according to national recommendations without any indication of treatment failure and at least 5 negative sputum cultures taken after completion of the initial phase at intervals of at least 30 days are available. According to the study protocol, cure was achieved if patients completed their treatment according to the treatment plan and consistently showed cultural evidence of the absence of pathogens in the sputum samples, i.e. in at least 5 sputum samples from the last 12 months of their treatment, using standardised methods of quantitative pathogen detection in liquid culture. A single sample with pathogens in the sputum was allowed in the study according to the WHO 2008 definition, provided that three consecutive sputum samples analysed at least 56 days apart showed absence of pathogens again.
The endpoint of cure is based on sputum culture conversion, which is an objectively measurable and valid parameter defined by the WHO, provided that adequate sputum culture was methodically collected. The operationalisation corresponds to the WHO criteria valid at that time. The updated WHO criteria (2013) assume a cure if treatment was completed according to national standards as planned, with no evidence of failure, and there were at least three consecutive negative culture results after the intensive treatment period (i.e. during continuation of treatment with anti-TB base therapy), with samples obtained at least 30 days apart. The change in the WHO criteria due to the update thus essentially refers to a lower number of negative culture findings required for a cure, so that the limitation in the operationalisation due to the reference to the older WHO definition in study 213 is assessed as minor.
At week 130, there was no statistically significant difference in the percentage of patients with a cure.

Clinical signs and symptoms

In study 213, the changes in the clinical signs and symptoms "cough", "haemoptysis", "dyspnoea", "chest/thoracic pain", "night sweats", "weight loss", "appetite loss" and "feverish feeling" were recorded over the course of the study. For this purpose, the study staff recorded whether certain signs or symptoms were present or absent since the last visit on the basis of physical examinations, laboratory tests, X-ray examinations and patient reports of complaints and, if they were present, assessed the frequency (sometimes, often, always) and intensity (mild, moderate, severe). No data was available on the specific operationalisation of the frequency characteristics. No results could be identified for the parameter "weight loss".
For the clinical signs and symptoms "cough", "haemoptysis", "dyspnoea", "chest/thoracic pain", "night sweats", "appetite loss" and "feverish feeling", descriptive data were collected at the time of screening and visits until the end of OBR treatment. In relation to the ITT

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population, a sufficiently high percentage of subjects could be included in the evaluation up to month 18. Both treatment arms showed a reduction in symptomatology over the course of the study until month 18. However, a comparative analysis using effect estimators was not presented.
Therefore, conclusions on the extent of additional benefit cannot be derived for this endpoint.

Quality of life

Data on quality of life were not assessed in the study 213.

Side effects

The assessment of AEs was continuous throughout the study. The AEs that occurred during treatment were evaluated. The AEs evaluated 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. A study-individual gradation of the severity according to the impairment of the activities of daily living was carried out. The study classified impairments that lead to inability to work or to limitations in normal activities of daily living as severe AEs. No justification was provided as to why these impairments were classified as severe in the context of MDR-TB disease, and the study's own gradation according to severity was thus not entirely comprehensible. In addition, it was not explained why the chosen operationalisation assessed fewer severe AEs than serious AEs.

Unaccounted for uncertainties in the operationalisation, there were no statistically significant differences between the treatment arms in the evaluation of serious or severe AEs and AEs that led to discontinuation of study medication.

No AEs of special interest were defined and evaluated.

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Overall assessment / conclusion

For delamanid as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability, there are results on mortality, morbidity and side effects based on the phase III RCT 213.

In summary, there is no statistically significant difference in the endpoint category of mortality.

In the morbidity category, the endpoints "cure" and "clinical signs and symptoms" were identified as patient-relevant and used for the benefit assessment. There are no statistically significant differences between the treatment arms.
Data on quality of life were not assessed in the study.
Likewise, in the side effects category, there were no statistically significant differences between the treatment arms.

In summary, no conclusions on the extent of additional benefit can be derived from the data. A quantitative assessment of the extent of the effect and a quantification of the additional benefit according to the categories "minor", "considerable" or "major" on the basis of the data presented is not possible. Taking into account the severity of the disease, the written statements and the oral hearing, the G-BA classifies the extent of additional benefit of delamanid in the treatment of adult patients with pulmonary multi-drug resistant tuberculosis (MDR-TB), when an effective treatment regimen cannot otherwise be composed for reasons of resistance or intolerance, as non-quantifiable on the basis of the criteria in Section 5, paragraph 7 AM-NutzenV since the scientific data does not allow quantification.

Significance of the evidence

For RCT 213 used for the benefit assessment, the risk of bias at study level is assessed as low.

Uncertainties exist in the randomised study population, which is why no evidence of MDR-TB could be provided by liquid culture at baseline for almost one third of the study participants. Another uncertainty regarding the study conducted from 2011 to 2016 is due to the fact that the antibiotics used in the study do not reflect the current German standard of care according to the guideline recommendations and thus the transferability of the study to the current German healthcare context is questionable.

In the overall assessment, this results in a hint for a non-quantifiable additional benefit with regard to the significance of the evidence, since the scientific data does not allow quantification.

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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

Study 233 used for the benefit assessment is an open-label, uncontrolled study to investigate the efficacy, safety and pharmacokinetics of delamanid in children and adolescents from birth to 17 years of age with a confirmed or suspected diagnosis of MDR-TB. In the six-month treatment phase, patients were treated with age-dependent doses of delamanid and an OBR. In the post-treatment and follow-up phase until month 24, treatment was reduced to OBR. The 37 patients enrolled in the study were divided into four age groups (0-2, 3-5, 6-11, 12-17 years). Only the age group of 3-5 year olds is considered relevant for the benefit assessment. The results of the other age groups were not taken into account, as the delamanid dosage in these was not or for the most part not as intended in the product information. The pharmaceutical company also presented the results of the multicentre, open-label, uncontrolled, pharmacokinetic phase I study 232 in the dossier. In this study, patients were treated with delamanid plus OBR for 10 days. The 37 patients who completed study 232 were treated further in the follow-up study 233. Due to the duration of use of study 232, which is not in line with the product information, and the short observation period, only the results of study 233 are used for the benefit assessment.

As a basis for the present benefit assessment, the results of the age group of 3 to 5-year-olds of study 233 are shown below.

Mortality

Overall survival

Overall mortality was recorded in the study 233. At the end of the study in month 24, one subject in the age group 3-5 years had died and one subject was lost to follow-up. Due to the small sample size, low number of events and lack of comparison, the effect of delamanid on mortality in the paediatric population cannot be conclusively assessed.

Morbidity

Cure

The treatment outcome was recorded by the medical investigators 24 months after administration of the first dose of delamanid. The treatment outcome was assessed according to the WHO outcome definition for the treatment of patients with MDR-TB. Three of the twelve study participants were recorded as cured at the end of the study. However, there are gaps in the description of the operationalisation. The WHO document to which the classification of treatment outcomes refers is not described. It thus remains open which criteria were applied and whether they were applied equally to children and adolescents. In particular, the paucibacillary form of TB and the difficulty in providing sputum samples can make cultural detection of TB, and thus detection of cure, much more difficult in children.

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Clinical signs and symptoms

The presence of clinical signs and symptoms of TB disease was assessed by study staff during the course of study 233. However, there are gaps in the description of the operationalisation. It is not described how the assessment was conducted, e.g. by means of an interview or a questionnaire, and who provided information. Furthermore, it is unclear to which period and which severity the signs and symptoms refer to and whether these are newly occurring symptoms or those that have already existed for some time. The parameters "weight loss" and "failure to thrive" are not further defined. The validity of the signs and symptoms recorded cannot be conclusively assessed due to the ambiguities in the survey and the definition of signs and symptoms; they are therefore presented additionally in the benefit assessment. On day 182, after completion of delamanid treatment, the clinical sign "night sweats" and the sign "appetite loss" were recorded once for the 12 study participants.

Quality of life

Data on quality of life were not assessed in the study 233.

Side effects

AEs were collected in study 233 from the time of first administration of delamanid until day 365 for each patient. The AEs that occurred during treatment were evaluated. AEs collected 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. No AEs of special interest were defined and evaluated.

AEs that occurred between the time of enrolment in the study and the start of study medication were not recorded. The patients in study 233 are subjects who have already been pretreated with delamanid in study 232. It cannot be ruled out that AEs that persisted until the start of study 233 already occurred during treatment with delamanid in study 232 and thus cannot be depicted as AEs.

Until day 365, severe AEs occurred in about 8% and serious AEs in 17%. In none of the subjects did AEs lead to discontinuation of delamanid therapy.

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Overall assessment

For delamanid indicated as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in 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, there are results on mortality, morbidity and side effects based on the open-label, uncontrolled study 233. For the benefit assessment, only the study results of the age group of 3 to 5-year-olds were used, as the dosage in the other age groups was not in line with the product information.

There was one death in the study 233.

In the endpoint category of morbidity, the endpoints "cure" and "clinical signs and symptoms" were recorded. Due to limitations with regard to operationalisation, the single-arm study design and the small number of cases, no conclusive statements could be made in these endpoint categories. In summary, no conclusions on the extent of additional benefit can be derived from the data on morbidity.

Furthermore, no data on quality of life were assessed.

Due to the small sample size, the low number of events and the lack of comparisons, it is not possible to derive any conclusions on the extent of the additional benefit from the data on side effects.

Due to the lack of comparator data from the single-arm study 233, the G-BA classifies the extent of additional benefit of delamanid in the treatment of pulmonary multi-drug resistant tuberculosis (MDR-TB) in 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, on the basis of the criteria in Section 5 paragraph 7 AM-NutzenV, taking into account the severity of the disease, the written statements and the oral hearing, as non-quantifiable since the scientific data does not allow quantification.

Significance of the evidence

There is a high risk of bias at study-level for the 233-study presented due to the single-arm, open-label study design. No comparator studies were presented. In the overall assessment, the above-mentioned uncertainties regarding the significance of the evidence result in a hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment for the active ingredient delamanid following repeal of the exemption due to turnover according to Section 35a, paragraph 1a SGB V. Deltyba was approved as an orphan drug.

The therapeutic indication assessed here is as follows:

"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

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body weight of at least 10 kg when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. "

Two patient groups were distinguished for the benefit assessment:

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

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

Patient group a)

For delamanid as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability, there are results on mortality, morbidity and side effects based on the phase III RCT 213.

In summary, there are no statistically significant differences in the three endpoint categories. Data on quality of life were not assessed in the study. The risk of bias at the study level was estimated to be low. In the overall assessment, a hint for a non-quantifiable additional benefit is identified for this patient group since the scientific data does not allow quantification.

Patient group b)

For delamanid as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in 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, there are results on mortality, morbidity and side effects based on the open-label, uncontrolled study 233. For the benefit assessment, only the study results of the age group of 3 to 5-year-olds were used, as the dosage in the other age groups was not in line with the product information.

There was one death in the study 233. Due to the small sample size, the low number of events and the lack of comparisons, the data on the endpoint categories of morbidity and side effects also do not allow any conclusions to be drawn on the extent of the additional benefit. No data on quality of life were assessed.

In the overall assessment, a hint for a non-quantifiable additional benefit is identified for this patient group since the scientific data does not allow quantification.

2.2 Number of patients or demarcation of patient groups eligible for treatment

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

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The information on the number of patients is based on the target population in statutory health insurance (SHI).

In order to ensure a consistent analysis of the patient numbers taking into account the most recent resolution (15 January 2019) on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication of pulmonary multi-drug resistant tuberculosis (MDR-TB) in adults, the G-BA uses the derivation of the target population used as a basis in the resolution on the benefit assessment of bedaquiline.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

In order to ensure a consistent analysis of the patient numbers taking into account the most recent resolutions (20 August 2020 and 16 September 2021) on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V in the present therapeutic indication of pulmonary multi-drug resistant tuberculosis (MDR-TB) in children and adolescents, the G-BA uses the derivations of the target population used as a basis in the resolutions on the benefit assessment of bedaquiline.

2.3 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.

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2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2022).

Treatment period:

The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

The use of delamanid is limited to 24 weeks.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Patient populations a) and b)				
Delamanid	2 x daily for 24 weeks	168	1	168

Consumption:

For the calculation of dosages depending on body weight, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were applied (average body weight of 17-year-olds: 67.0 kg).[2]

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Patient population a)					
Delamanid	100 mg	200 mg	4 x 50 mg	168	672 x 50 mg
Patient population b)					
Delamanid	Patients ≥ 10 kg to < 20 kg				
	25 mg	50 mg	2 x 25 mg	168	336 x 25 mg

[2] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	Patients ≥ 20 kg to < 30 kg				
	50 mg; 25 mg	75 mg	3 x 25 mg	168	504 x 25 mg
	Patients ≥ 30 kg to < 50 kg				
	50 mg	100 mg	2 x 50 mg	168	336 x 50 mg
	Patients ≥ 50 kg				
	100 mg	200 mg	4 x 50 mg	168	672 x 50 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Delamanid 50 mg	48 FCT	€ 1,800.30	€ 1.77	€ 102.22	€ 1,696.31
Delamanid 25 mg TOS[3]	-	-	-	-	-
Abbreviations: FCT = film-coated tablets; TOS = tablets for oral suspension					

LAUER-TAXE® last revised: 15 April 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

[3] 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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Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 3 November 2021, the pharmaceutical company submitted a dossier for the benefit assessment of delamanid to the G-BA.

The benefit assessment of the G-BA was published on 15 February 2022 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 9 March 2022.

The oral hearing was held on 28 March 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 26 April 2022, and the draft resolution was approved.

At its session on 5 May 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	22 February 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	15 March 2022	Information on written statements received; preparation of the oral hearing
Subcommittee	28 March 2022	Conduct of the oral hearing

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Medicinal products		
Working group Section 35a	5 April 2022 20 April 2022	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	26 April 2022	Concluding discussion of the draft resolution
Plenum	5 May 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 5 May 2022

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

Prof. Hecken

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