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 Bedaquiline (reassessment after the deadline: pulmonary multidrug-resistant tuberculosis)

of 1 February 2024

Contents

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 € 30 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, paragraphs 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 approval 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 turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be 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 pharmaceutical company submitted a dossier for the early benefit assessment for the active ingredient bedaquiline to be assessed for the first time on 14 January 2019. For the resolution of 4 July 2019 made by the G-BA in this procedure, a limitation up to 30 June 2021 was pronounced. At the pharmaceutical company's request, this limitation was extended until 31 July 2023 by the resolution of the G-BA of 4 March 2021.

In accordance with Section 4, paragraph 3, No. 5 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of the medicinal product Sirturo recommences when the deadline has expired.

For this purpose, the pharmaceutical company submitted the dossier for the benefit assessment to the G-BA in due time on 31 July 2023 (Section 4, paragraph 3, no. 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO).

Sirturo for the treatment of pulmonary multidrug-resistant tuberculosis is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) Number 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 and probability of the additional benefit are assessed on the basis of the approval 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 costs and patient numbers. The benefit assessment was published on 1 November 2023 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 G23-18) 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 evaluated the studies relevant for the approval with regard to 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 bedaquiline.

1 General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Bedaquiline (Sirturo) in accordance with the product information

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.

2.1.2 Extent of the additional benefit and significance of the evidence

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

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

For bedaquiline as part of an appropriate combination therapy, there is a hint for a considerable additional benefit for adult patients with pulmonary multidrug-resistant tuberculosis for whom an effective treatment regimen cannot otherwise be composed for reasons of resistance or intolerance.

Justification:

The benefit assessment is based on the phase IIb approval study TMC207-C208 (Stage 2), which was already included in the initial resolution of 4 July 2019, and the supplementary phase III STREAM study (Stage 2).

Study C208 investigated the antibacterial activity, safety and tolerability of bedaquiline and placebo as part of a combination therapy (base therapy or background regime, BR) in newly diagnosed patients with pulmonary multidrug-resistant MDR-TB with a positive sputum smear. This is a 120-week, randomised, double-blind, multicentre, placebo-controlled study in a parallel group design, in which the patients enrolled were treated with bedaquiline or placebo as an "add on" to their ongoing base therapy for 24 weeks; they were then followed up for 96 weeks with continuation of the basic therapy until week 120. In the study, the patients (N=160) were randomised to the two study arms bedaquiline + BR (N = 79) or placebo + BR (N = 81) in a 1:1 ratio. The base therapy was specified prior to randomisation and was standardised as far as possible. It was designed as a combination therapy and preferably contained the 5 active ingredients kanamycin, ofloxacin, ethionamide, pyrazinamide and cycloserine/ terizidone. In the event of reduced availability of the medicinal product or intolerance to one of the active ingredients administered, substitutions could be made. In the study, the primary endpoint was defined as "time to absence of pathogens in the sputum" and important secondary endpoints included cure.

For the benefit assessment, the final analysis of the study with data cut-off at week 120 (data cut-off of 31.01.2012) for the ITT and safety population is mapped and considered for the

categories of morbidity and side effects. For the mortality category, the later data cut-off from 16.10.2012 is used as a basis.

Mortality

Overall mortality

Mortality was recorded in the C208 study and the long-term observation in the context of safety. By week 120, 10 deaths occurred in the bedaquiline arm (12.7%) and 3 deaths in the placebo arm (3.7%); the result is statistically insignificant.

The imbalance of deaths between the treatment groups initially remained unexplained and was the reason for limiting the resolution on bedaquiline to 4 July 2019 (see explanations below).

Morbidity

Cure (according to the WHO definition 2008)

The endpoint of 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.

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. At week 120, the percentage of patients who achieved a cure according to the 2008 WHO definition was significantly higher in the bedaquiline + BR arm. The high percentage of missing values at week 120 in both treatment arms leads to a possible bias at the endpoint level (study discontinuation): control group 38.3%; intervention group 36.7%). Furthermore, at the time of the final data cut-off at week 120, not all patients had completed the study. The percentage of patients who were not observed until week 120 is unclear.

Time to absence of pathogens in the sputum

The primary endpoint of the study C208 was the "time to absence of pathogens in the sputum".

At week 120, 61% of patients in the bedaquiline + BR arm and 36% of patients in the control arm achieved absence of pathogens in the sputum. There was a statistically significant faster conversion in the bedaquiline arm after 86 days compared to the control arm at 345 days.

The operationalisation of the endpoint in the study required demonstration of pathogen absence by two consecutive negative microbiological sputum cultures at a minimum interval

of 28 days. In the German S2k guideline2 for the treatment of drug-sensitive tuberculosis, three negative microscopic sputum samples are recommended before isolation is repealed.

The absence of pathogens is a basic prerequisite for lifting isolation because the risk of infection no longer exists. The length of time patients are isolated has an impact on quality of life and is patient-relevant. However, the pharmaceutical company did not collect data on quality of life or hospitalisation. The duration of isolation depends on other factors in addition to the absence of pathogens. It is therefore questionable to what extent the endpoint "time to absence of pathogens" 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 "absence of pathogens" with the endpoint "cure" presented. For this reason, the time to absence of pathogens endpoint is only presented additionally and is not used for the NB.

Relapse

In the final analysis of the study C208, the number of relapses was also recorded. Relapse was defined as a positive sputum culture after a patient had already been defined as converted. Patients were considered to have relapsed if they either had at least two consecutive sputum samples with Mycobacterium tuberculosis pathogens during the study and were subsequently unable to achieve confirmed absence of pathogens status, or if their last sputum sample showed pathogens again at the end of study or when the study was discontinued.

At week 120, 7.6% of patients in the intervention arm and 13.6% of patients in the control arm were diagnosed with a relapse; the difference between the treatment arms is statistically insignificant.

According to the information of the pharmaceutical company in the statement, a classification as "cure" before a "relapse" was not possible in the study C208. Uncertainties remain due to the operationalisation of the endpoint "relapse" carried out by the pharmaceutical company, as there is no reference to cure; a relapse was not only defined after previous cure, but already after previous conversion. There are also overlaps in the operationalisation of the endpoint "relapse" with the endpoint "cure".

Thus, against the background of the chosen operationalisation, the extent to which the endpoint "relapse" can provide information on the re-isolation of patients remains questionable. The endpoint "relapse" is only presented additionally and is not used for the BA.

Quality of life

No data on health-related quality of life were collected.

Side effects

Adverse events were collected from the first day until 30 days after the last dose. The median treatment period was 92 weeks in the bedaquiline arm and 94 weeks in the placebo arm. The safety population corresponds to the ITT population of the study C208.

At week 120, there was no statistically significant difference in the occurrence of severe AEs, SAEs and therapy discontinuations due to AEs between the bedaquiline + BR and placebo + BR arms.

2 German S2k guideline of the DZK (German Central Committee against Tuberculosis) and DGP (German Respiratory Society) from 2017: Tuberculosis in adulthood

For AEs of any severity by system organ class and preferred term with an incidence ≥ 10%, the most common AEs in both groups were "Nausea", "Vomiting" and "Arthralgia". Only the preferred terms "Diarrhoea" and "Tinnitus" showed a statistically significant difference in favour of bedaquiline + BR.

STREAM study (Stage 2)

Due to the uncertainties, particularly in the evaluations presented on mortality in the study C208, a final assessment of the additional benefit of bedaquiline was not possible with sufficient certainty. The benefit assessment resolution of 4 July 2019 was therefore limited in time so that the results of the comparator phase III STREAM study could be presented for a new benefit assessment.

The STREAM study is a multicentre, randomised, open-label, parallel-group phase III study in patients with MDR-TB, including subjects with rifampicin-resistant and isoniazid-sensitive TB. The study participants -were allocated to 4 study arms, which received different treatment regimens. The study consists of 2 parts: In stage 1, the long-term regimen (study arm A) was compared with the control regimen (study arm B). In stage 2, the two bedaquiline-containing regimens (study arms C and D) were each compared with the control regimen (study arm B).

For the benefit assessment, only the comparison of study arm C (bedaquiline arm) vs study arm B (control) of the STREAM study Stage 2 is considered. Study arm D is not included due to the different treatment duration. Study arm A is not considered since the comparison of study arm A (locally used WHO regimen) versus study arm B (control regimen) is part of the STREAM study Stage 1, which is not relevant for the benefit assessment.

A total of 588 subjects were enrolled in the study, 291 of whom (bedaquiline (arm C): n = 150; control (arm B): n = 141) were analysed in the MDR-TB population relevant to the assessment.

The STREAM study Stage 2 has several limitations, due to which the study is only used as a supplement:

- Study arms B and C are comparable with 40 weeks of treatment, including a 16-week intensive phase. However, the regular treatment duration with bedaquiline is 24 weeks according to the requirements in the product information. Only if a longer treatment duration "is considered necessary to achieve curative treatment can a longer treatment duration under close monitoring be considered".
- The treatment regimens of the two study arms differ in terms of the additional active ingredients used. In study arm B, kanamycin is also administered in the intensive phase of the treatment phase. In addition, moxifloxacin was administered in study arm B and levofloxacin from protocol version 8.0, while in study arm C only levofloxacin was administered. Thus, the comparator therapy is inconsistent over the duration of the study and it is unclear against which treatment regimen efficacy and safety are measured. Furthermore, the treatment regimens administered no longer correspond to the current therapy standard.
- 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 the control arm received bedaquiline as part of the salvage therapy. The percentage in the corresponding MDR-TB population is 11.3%.
- In the intensive phase (16 weeks) of the treatment phase, isoniazid was administered to all subjects in both the bedaquiline arm (arm C) and the control arm (arm B). According to the German S2k guideline, administration of high-dose isoniazid is only adequate in cases of proven low-level isoniazid resistance. It is unclear whether the study population was

treated appropriately since it is not possible to assess whether low-level isoniazid resistance was present in all subjects.

Overall, the STREAM study (Stage 2) thus has relevant limitations, which is why the study results cannot be directly considered for the assessment of the additional benefit of bedaquiline. In the present benefit assessment, the study C208 is therefore still used to derive the additional benefit. There is no evidence from the STREAM study (stage 2) to support the numerically increased overall mortality in the bedaquiline arm of the study C208, so that overall an increased mortality with bedaquiline cannot be assumed.

Overall assessment

For bedaquiline as part of a suitable combination therapy for the treatment of adult patients with pulmonary multidrug-resistant tuberculosis, if an effective treatment regimen cannot otherwise be composed for reasons of resistance or intolerance, results on mortality, morbidity and side effects are available on the basis of the pivotal phase II RCT C208, which are already known from the previous benefit assessment of bedaquiline in this therapeutic indication.

In the endpoint category of mortality, the study C208 did not show any statistically significant difference between the treatment arms. However, there were uncertainties due to the unexplained imbalance in deaths occurring in the bedaquiline arm compared to the placebo arm. Due to these uncertainties, the period of validity of the previous benefit assessment resolution on bedaquiline of 4 July 2019 was limited in order to present further comparator data, including on the safety profile of bedaquiline from the STREAM study (Stage 2). There is no evidence from the additionally presented STREAM study (Stage 2) that would support the numerically increased overall mortality in the bedaquiline arm of the study C208, so that overall an increased mortality with bedaquiline cannot be assumed.

However, the results of the STREAM study (Stage 2) can still not be used to assess the additional benefit of bedaquiline due to relevant limitations, including the selected treatment duration and different concomitant medication.

In the morbidity category, there was a statistically significant and important advantage for the bedaquiline-containing base therapy in the endpoint "cure according to WHO 2008" at week 120.

Data on quality of life were not assessed in the C208 study.

In terms of side effects, there were no statistically significant differences between the comparator arms with regard to the overall rates of serious adverse events (CTCAE grade ≥ 3) or SAEs.

Overall, there was a significant advantage of bedaquiline in the morbidity endpoint category. The G-BA categorised the extent of the additional benefit of bedaquiline for the treatment of multidrug-resistant tuberculosis in adults as considerable on the basis of the criteria in Section 5, paragraph 8 in conjunction with Section 5, paragraph 7, sentence 1, numbers 1 to 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

Significance of the evidence

As in the initial resolution of 4 July 2019, this assessment is based on the results of the placebo-controlled, direct comparator RCT C208. Uncertainties exist due to the high percentage of missing values at week 120 as a result of the high rate of study discontinuations of almost 40%. This leads to a potential risk of bias. Furthermore, the transferability of the study results

to the current healthcare context is difficult, as treatment regimens for the treatment of MDR-TB that differ from the study medication have now become established.
Against this background, the reliability of data is classified under the "hint" category.

2.1.3 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient bedaquiline due to the expiry of the limitation of the resolution of 4 July 2019. The evaluation refers exclusively to adult patients with pulmonary multidrug-resistant tuberculosis.

The benefit assessment is based on the phase IIb approval study TMC207-C208 (Stage 2), which was already included in the initial resolution of 4 July 2019, and the supplementary phase III STREAM study (Stage 2).

In the endpoint category of mortality, the study C208 did not show any statistically significant difference between the treatment arms. However, there were uncertainties due to the unexplained imbalance in deaths occurring in the bedaquiline arm compared to the placebo arm. Due to these uncertainties, the period of validity of the previous benefit assessment resolution on bedaquiline of 4 July 2019 was limited in order to present further comparator data, including on the safety profile of bedaquiline from the STREAM study (Stage 2). There is no evidence from the additionally presented STREAM study (Stage 2) that would support the numerically increased overall mortality in the bedaquiline arm of the study C208, so that overall an increased mortality with bedaquiline cannot be assumed.

However, the results of the STREAM study (Stage 2) can not be used to assess the additional benefit of bedaquiline due to relevant limitations, including the selected treatment duration and different concomitant medication.

In the morbidity category, there was a statistically significant and important advantage for the bedaquiline-containing base therapy in the endpoint "cure according to WHO 2008" at week 120.

Data on quality of life were not assessed in the C208 study.

In terms of side effects, there were no statistically significant differences between the comparator arms with regard to the overall rates of serious adverse events (CTCAE grade ≥ 3) or SAEs.

Overall, there was a significant advantage of bedaquiline in the morbidity endpoint category. The G-BA categorised the extent of the additional benefit of bedaquiline for the treatment of multidrug-resistant tuberculosis in adults as considerable on the basis of the criteria in Section 5, paragraph 8 in conjunction with Section 5, paragraph 7, sentence 1, numbers 1 to 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV). The reliability of data is classified in the category "hint".

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

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

The information is based on the data from the benefit assessment resolution on bedaquiline of 4 July 2019. The calculation of the size of the target population represents an overestimate overall, but is considered a better estimate than the patient number calculated in the

pharmaceutical company's current dossier, as there are indications that the number of patients with MDR-TB is likely to be higher due to migration flows.

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 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.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 January 2024).

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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

The regular treatment duration with bedaquiline is 24 weeks according to the product information.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Bedaquiline	Week 1 - 2: 1 x daily Week 3 - 24: 3 x weekly	80	1	80

Consumption:

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					
Bedaquiline	Week 1 - 2: 400 mg Week 3 - 24: 200 mg	200 – 400 mg	2 – 4 x 100 mg	80	188 x 100 mg

Costs:

Costs of the medicinal products:

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	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					
Bedaquiline	24 tablets	€ 3,719.43	€ 2.00	-	€ 3,717.43

LAUER-TAXE® last revised: 15 January 2024

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.

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.

No additionally required SHI services are taken into account for the cost representation.

2.5 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

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient:

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible

concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of

medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

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.

Justification for the findings on designation in the present resolution:

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 designated medicinal products concern in each case an active ingredient which may be used in combination therapy with the assessed medicinal product in the context of a therapeutic indication specified in the product information for the assessed medicinal product. This therapeutic indication is delamanid according to the requirements in the product information.

For the designated medicinal products, the prerequisites of Section 35a, paragraph 3, sentence 4 SGB V are fulfilled and, according to the requirements in the product information, there are no reasons for exclusion that prevent a combination therapy with the assessed medicinal product.

References:

- Product information for bedaquiline (Sirturo); SIRTURO 20 mg/100 mg tablets; Last revised: February 2023
- Product information for delamanid (Deltyba); Deltyba 50 mg film-coated tablets; Last revised: July 2023

Supplement to Annex XIIa of the Pharmaceuticals Directive

Since the resolution under I.5 mentions medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V, which can be used in a combination therapy with the assessed active ingredient in the therapeutic indication of the resolution, the information on this designation is to be added to Annex XIIa of the Pharmaceuticals Directive and provided with patient-group-related information on the period of validity of the designation.

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 31 July 2023, the pharmaceutical company submitted a dossier for the benefit assessment of bedaquiline to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 5 VerfO.

The benefit assessment of the G-BA was published on 1 November 2023 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 statements was 22 November 2023.

The oral hearing was held on 11 December 2023.

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 was discussed at the session of the subcommittee on 23 January 2024, and the proposed resolution was approved.

At its session on 1 February 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	24 September 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	5 December 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	11 December 2023	Conduct of the oral hearing
Working group Section 35a	19 December 2023 16 January 2024	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	23 January 2024	Concluding discussion of the draft resolution
Plenum	1 February 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 1 February 2024

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

Prof. Hecken