Justification

Gemeinsamer Bundesausschuss

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

of 4 July 2019

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 a rare disease (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 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 evaluation 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. Only the extent of the additional benefit is to be demonstrated.

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 retail prices 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 approval studies by the G-BA.

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 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 forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient bedaquiline was listed for the first time on 15 May 2014 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

The pharmaceutical company has submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 1 VerfO on 14 May 2014.

The medicinal product Sirturo with the active ingredient bedaquiline was launched onto the market on 15 May 2014 in a package size which exceeds the largest package size specified by the German Packaging Size Ordinance in accordance with Section 31 paragraph 4 sentence 1 SGB V. According to Section 31 paragraph 4 sentence 2 SGB V, this means that pursuant to Section 31 paragraph 1 sentence 1 SGB V, the medicinal product is not covered by and may not be paid for by the statutory health insurance. Sirturo® was therefore neither prescribable nor reimbursable at that time. Since Section 35a paragraph 1 sentence 1 SGB V stipulates that a medicinal product must be reimbursable for a benefit assessment to be performed on a new active ingredient and Sirturo® did not fulfil this requirement, a resolution was passed, dated 21 August 2014 (Federal Gazette, BAnz AT 2 September 2014 B3), to discontinue the benefit assessment procedure.

In a letter dated 14 July 2015, the pharmaceutical company informed the G-BA that it planned to market a smaller, reimbursable package size for the active ingredient bedaquiline under a new German Pharmaceutical Central Number (PZN).

As the pharmaceutical company would thus have fallen within the applicability of Section 35a, it applied for an exemption from the obligation to submit a dossier pursuant to Section 4 of the Rules of Procedure.

By resolution dated 3 September 2015, the pharmaceutical company was exempted from the obligation to submit a dossier as per Chapter 5, Section 5 of the Rules of Procedure of the Federal Joint Federal (VerfO) and the proprietary medicinal product concerned was exempted from the benefit assessment in accordance with the provisions of Chapter 5 of the VerfO.

On 1 June 2016, the pharmaceutical company introduced a smaller, refundable package size under a new German Pharmaceutical Central Number (PZN).

In the course of the standard review by the G-BA as to whether the factual prerequisites for the exemption according to Section 35a paragraph 1a SGB V still applied, it was determined that the expenditure of statutory health insurance funds exceeded €1,000,000 within 12 calendar months. The pharmaceutical company was requested by letter dated 4 October 2018 to submit a dossier in accordance with Chapter 5, Section 12, no. 1 in conjunction with Section 5 paragraph 7 of the VerfO within three months of being requested to do so by the Federal Joint Committee.

The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 1 VerfO on 14 January 2019.

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

According to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be already proven. The extent of the additional benefit is 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 15 April 2019 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 evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G19-01) 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.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

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 multi-drug-resistant tuberculosis [*multi-drug-resistant Mycobacterium tuberculosis* (MDR-TB)] in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

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

2.1.2 Extent of the additional benefit

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

For bedaquiline as part of an appropriate combination regimen for pulmonary multi-drug-resistant tuberculosis [multi-drug-resistant Mycobacterium tuberculosis (MDR-TB)] there is a considerable additional benefit in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

Justification:

The benefit assessment was performed based on the pivotal phase IIb authorisation study TMC207-C208 (Stage 2).
This study investigated the antibacterial activity, safety and tolerability of bedaquiline and placebo as part of a combination regimen (background regimen, BR) in newly diagnosed patients with pulmonary multi-drug-resistant tuberculosis MDR-TB with a positive sputum smear. The study was a 120-week, randomised, double-blind, multicentre, placebo-controlled study, designed with parallel groups, in which the enrolled patients were treated for 24 weeks

1 General Methods, version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

with bedaquiline or placebo as an “add on” to their ongoing background regimen treatment. Subsequently, patients were followed up for 96 weeks up to week 120 with continuation of the background regimen. In the study, patients (N = 160) were randomly assigned at a ratio of 1:1 to the two study arms bedaquiline+BR (N=79) and placebo+BR (N=81). The background regimen treatment was specified prior to randomisation and was, generally, standardised. It was designed as a combination regimen and preferentially comprised the five active ingredients kanamycin, ofloxacin, ethionamide, pyrazinamide and cycloserine/terizidone. If there was a shortage of or patients were intolerant to one of the active ingredients administered, this could be substituted. The primary endpoint defined in the study was "time to pathogen-free sputum", with secondary endpoints including, importantly, "cure".

For the categories "mortality" and "side effects" the benefit assessment detailed and took into account the final analysis of the study, with a data cut-off at week 120 (data cut-off 31 January 2012) for the ITT and safety populations. The mortality category is adjusted to reflect the later data cut-off of 16 October 2012 (addendum to the final analysis on mortality).

In the dossier, the pharmaceutical company also presented the results of the non-randomised, open, single-arm phase II study C209, the early access programme C3001 and the retrospective South African cohort study. Due to the very low meaningfulness of uncontrolled data and the identical duration of the C208 pivotal study and the C209 and C3001 studies, the latter were not considered in the benefit assessment, in consideration of the available RCT data from the C208 study. The data from the retrospective cohort study were also disregarded due to its very low degree of evidence and potential sample bias.

Mortality

Overall survival

In the context of safety, mortality was assessed using the C208 study and long-term monitoring. Up to week 120, 10 deaths occurred in the bedaquiline arm (12.7%) and 3 deaths in the placebo arm (3.7%); this result is not statistically significant.
The imbalance of deaths between treatment groups cannot, as yet, be explained and is the subject of further research, as stipulated as a condition under the conditional marketing authorisation.

Morbidity

Cure (according to the 2008 WHO definition)
The endpoint "cure" was operationalised as a secondary endpoint largely based on the WHO 2008 definition of "cure". Under the 2008 WHO definition, a cure is achieved when treatment has been terminated in accordance with national recommendations, with no indication of treatment failure and after at least five negative sputum cultures, taken at least 30 days apart after completion of the initial phase. According to the study protocol, patients were considered to be cured if they had completed their treatment according to the treatment plan and sputum samples taken from them were consistently free of pathogens, i.e. at least 5 samples from the last 12 months of treatment were free, as determined by standardised techniques for quantitative detection of pathogens in liquid culture. The 2008 WHO definition allows for a single sample to contain pathogens in the sputum, provided that three consecutive sputum samples, analysed at least 56 days apart, reveal no pathogens.
Achieving a cure is based on sputum culture conversion, which is an objectively measurable and valid parameter defined by the WHO, as long as sputum cultures have been obtained in

a methodologically appropriate manner. At week 120, the percentage of patients who had achieved a cure according to the WHO 2008 definition was significantly higher in the bedaquiline+BR arm at 57% compared to the placebo+BR control arm at 33.3% [HR: 1.67 [95%-CI: 1.17; 2.38], p=0.0055]. The high number of missing data points at week 120 in both treatment arms results in a potential endpoint bias (control group 38.3 %; intervention group 36.7 %). In addition, 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.

Regardless of the methodological uncertainties described above, the significant difference as established between bedaquiline-containing combination regimen and placebo+background-regimen therapy for the “cure” endpoint is estimated to be considerable, given the current extent of resistances.

Time to pathogen-free sputum

The primary endpoint of C208 study was "time to pathogen-free sputum".

At week 120, 61% of patients in the bedaquiline+BR arm and 36% of patients in the control arm had achieved pathogen-free sputum. There was a statistically significant faster conversion in the bedaquiline arm after 86 days than in the control arm after 345 days (HR [95%-CI]: 2.01 [1.29; 3.14]; p = 0.002).

The study's operationalisation of the endpoint required two consecutive microbiological sputum cultures free of pathogens at a minimum interval of 28 days. The German S2k guidelines[2] for the treatment of drug-sensitive tuberculosis recommend three microscopically negative sputum samples before isolation is lifted.

Absence of pathogens eliminates the risk of contagion and is therefore a prerequisite for lifting isolation. Isolation duration has an influence on quality of life and is relevant for patients. However, the pharmaceutical company neither collected quality of life nor hospitalisation data. The duration of isolation depends not only on the absence of pathogens but also on other factors. It is therefore debatable to what extent the endpoint "time to pathogen-free sputum" alone is able to yield information on the actual duration of patient isolation in the current operationalisation. In addition, it should be noted that there are overlaps in the operationalisation of the endpoints "pathogen-free sputum" and "cure".

Relapse

The final analysis of the C208 study additionally surveyed the number of relapses. Relapse was defined as a positive sputum culture after a patient had already been defined as converted. Relapse in patients was defined as either having at least two consecutive sputum samples containing *Mycobacterium tuberculosis* pathogens during the study and not subsequently achieving confirmed pathogen-free status, or the reappearance of pathogens in the final sputum sample at the end of the study or after terminating participation in the study.

2 German S2k guidelines issued in 2017 by the German Central Committee against Tuberculosis (DZK) and the German Respiratory Society (DGP): Tuberkulose im Erwachsenenalter [*Tuberculosis Guideline for Adults*]

At week 120, 7.6% of patients in the intervention arm and 13.6% of patients in the control arm were diagnosed as relapsed; the difference between the treatment arms is not statistically significant.

The pharmaceutical company specified in its statement that in the C208 study it was not possible for patients to be classified as "cured" and then subsequently as "relapsed". The pharmaceutical company's operationalisation of the endpoint "relapse" results in uncertainties, as this does not relate the endpoint with a cure; a relapse was not defined as subsequent to a preceding cure, but as subsequent to a preceding conversion. There are also overlaps in operationalisation of the endpoints "relapse" and "cure".

The "relapse" endpoint's chosen operationalisation, therefore, also leads to uncertainties in how accurately it can provide information on patient isolation.

Quality of life

Data on patients' quality of life were not collected in the C208 study.

Side effects

Adverse events were recorded from day one until 30 days after the last dose. The median treatment duration was 92 weeks in the bedaquiline arm and 94 weeks in the placebo arm. The safety population is equivalent to the C208 study's ITT population.

AEs, serious AEs, SAEs, withdrawal due to AE/death

By week 120, similar frequencies of AEs, severe AEs (AEs with a severity grade of ≥ 3), and withdrawals from the study were reported for both treatment groups. More serious adverse events in the bedaquiline+BR arm were reported than in the placebo+BR arm, but the difference was not statistically significant. Adverse events leading to treatment discontinuation were likewise recorded more frequently in the bedaquiline+BR arm than in the placebo arm. Data on deaths were recorded for safety reasons.

In the C208 study, the most common SOC and PT adverse events with a cut-off incidence of ≥ 10% in one of the arms and a difference of at least 10% points (rounded) between the arms were diarrhoea (bedaquiline+BR versus placebo+BR: 6.3% versus 18.5%), dyspepsia (5.1% versus 14.8%), nervous system disorders (50.6% versus 40.7%), arthralgia (36.7% versus 22.9%) and tinnitus (3.8% versus 13.6%).

AEs of special interest

The pharmaceutical company classified acute pancreatitis, rhabdomyolysis/myopathy, severe skin events, Torsades de Pointes/QT prolongation and selected drug-related liver diseases as AEs of special interest. For these, no statistically significant differences between the two study arms were observed at week 120.

Overall assessment

The pivotal phase II RCT C208 provides evidence on mortality, morbidity and adverse events for bedaquiline as part of an appropriate combination regimen for the treatment of adult patients with pulmonary multi-drug-resistant tuberculosis [*multi-drug-resistant Mycobacterium*

tuberculosis (MDR-TB)], when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

In summary, no statistically significant difference was observed in the mortality endpoint category. However, based on the available data, uncertainties remain regarding the safety of bedaquiline due to the unexplained difference in the number of deaths in the bedaquiline arm compared to the placebo arm. Further comparative data, including data on the safety profile of bedaquiline, are expected from the ongoing phase III STREAM study; the results of this study must also be submitted to the regulatory authorities.

Of the statistically significant differences revealed in the morbidity category, a background regimen containing bedaquiline was shown to be particularly advantageous for the endpoint "cure as per WHO 2008" at week 120. In the context of high levels of drug resistance, the drug was found to have considerable additional benefit in the morbidity category.

Data on patients' quality of life were not collected in the study.

With regard to side effects, no statistically significant differences in rates of serious adverse events (CTCAE grade of severity ≥ 3) (SAEs) were found between the comparison arms.

From an overall perspective, however, the uncertainties regarding mortality do not call into question the significant advantages of bedaquiline associated with morbidity.

On the basis of the benefit assessment, taking into account the severity of the disease, the written statements, the oral hearing and against the background of high levels of drug resistance, the G-BA classifies, on the basis of the criteria in Section 5 paragraph 7 AM-NutzenV, the extent of the additional benefit for bedaquiline as a component of a background regimen to be considerable.

2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of bedaquiline finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment pursuant to Section 35a paragraph 1 SGB V.

To assess the additional benefit of bedaquiline, the pharmaceutical company submitted the pivotal phase IIb RCT C208 study on bedaquiline as part of an appropriate combination regimen for the treatment of adult patients with pulmonary multi-drug-resistant tuberculosis [*multi-drug-resistant Mycobacterium tuberculosis* (MDR-TB)], when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.

The current benefit assessment cannot conclusively establish with sufficient certainty an additional benefit for bedaquiline, in particular with regard to mortality. In contrast to the benefit assessment's mortality data cut-off and the information in section 5.1 of the product information for Sirturo, EPAR analyses (final analysis week 120 (ITT population), data cut-off 31 January 2012[3]) established a significant disadvantage for bedaquiline (10 deaths in the bedaquiline

3 https://www.ema.europa.eu/documents/assessment-report/sirturo-epar-public-assessment-report_en.pdf

arm and 2 deaths in the placebo arm). The imbalance of deaths between treatment groups cannot, as yet, be explained and is the subject of further research, as stipulated as a condition under the conditional marketing authorisation. The results of the ongoing phase III STREAM study must be submitted to the EMA by Q4 2023 at the latest. These phase III results are also relevant for the benefit assessment, as specified in Section 35a SGB V. To enable these relevant data to be employed in assessing patient-relevant endpoints for treatment of MDR-TB with bedaquiline, the G-BA considers it appropriate to limit the period of validity of this resolution to 30 June 2021, even if, at this time, only an interim analysis is expected for the above-named study.
After expiry of this time limit, the submitted dossier for the re-evaluation of benefit must include the results of the comparative phase III STREAM study for all patient-relevant endpoints. The G-BA considers two years to be sufficient in this respect.

The possibility that a benefit assessment for bedaquiline may be carried out at an earlier point in time for other reasons (*cf.* Chapter 5, Section 1 paragraph 2, numbers 2–6 VerfO) remains unaffected hereof. In accordance with Section 3 no. 5 AM-NutzenV in conjunction with Chapter 5 Section 1 paragraph 2 no. 7 VerfO, the procedure for assessing the benefit of the medicinal product bedaquiline shall recommence once the time limit has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of bedaquiline in relation to the appropriate comparator therapy (Section 4, paragraph 3, no. 5 AM-NutzenV in conjunction with Chapter 5 Section 8, no. 5 VerfO).

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the medicinal product Sirturo® comprising the active ingredient bedaquiline, after sales of the drug exceeded the turnover limit of €1 million. As an orphan drug, bedaquiline has received a conditional marketing authorisation.

The current assessment was conducted for the therapeutic indication “as part of an appropriate combination regimen for pulmonary multi-drug-resistant tuberculosis [*multi-drug-resistant Mycobacterium tuberculosis* (MDR-TB)] in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.”

This benefit assessment is based on the 120-week, placebo-controlled phase IIb pivotal authorisation study TMC207-C208 (Stage 2), in which MDR-TB patients were treated for 24 weeks with an "add-on" to their ongoing background regimen of either bedaquiline or placebo, each as a component of a combination regimen.

Analysis establishes a statistically significant, considerable advantage at week 120 for bedaquiline+background regimen (BR) over placebo+BR in the morbidity category, in particular for the endpoint "Cure as per WHO definition". No health-related quality of life data was collected. No statistically significant differences were demonstrated in overall rates in the mortality and side effects categories. However, based on the available data, uncertainties remain regarding the safety profile of bedaquiline due to the unexplained discrepancy in the number of deaths in the bedaquiline arm compared to the placebo arm. However, the uncertainties regarding mortality do not call into question the significant advantages of bedaquiline associated with morbidity.

A considerable additional benefit is derived for bedaquiline as part of a combination regimen for pulmonary multi-drug-resistant tuberculosis. The validity of the resolution is limited to 30 June 2021 owing to pending results from comparative studies.

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).
These are based on the data from the pharmaceutical company's dossier. From an overall perspective, the calculated target population represents an overestimation; as indicated in the product information, bedaquiline is only indicated for MDR-TB patients for whom an effective treatment regimen cannot otherwise be formulated due to resistance or intolerance.

2.3 Requirements for a quality-assured application

The requirements of the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Sirturo® (active ingredient: bedaquiline) at the following publicly accessible link (last access: 12 April 2019):
https://www.ema.europa.eu/documents/product-information/sirturo-epar-product-information_en.pdf

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

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

This medicinal product was authorised under "specific conditions". This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

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 June 2019).

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 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.

Treatment with Sirturo® may not exceed 24 weeks.

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	Weeks 1–2: 1 x daily Weeks 3–24: 3 x per week	80	1	80

Usage and consumption:

Designation of the therapy	Dosage	Dose/ patient/ day of treatment	Consumption based on medication potency/ treatment day	No. treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Bedaquiline	Weeks 1–2: 400mg Weeks 3–24: 200mg	200 – 400mg	2-4 × 100mg	80	188 × 100mg

Costs:

Costs of the medicinal product:

Designation of the therapy	Package 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	€4,338.23	€1.77	€244.48	€4,091.98

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 June 2019

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.

Because there are no regular differences in the necessary use of medical treatment or 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

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 14 January 2019, 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, no. 6 VerfO.

The benefit assessment of the G-BA was published on 15 April 2019 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 6 Mai 2019.

The oral hearing was held on 27 May 2019.

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 statements received and the oral hearing were discussed at the session of the subcommittee on 25 June 2019, and the proposed resolution was approved.

At its session on 4 July 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	9 April 2019	Information of the benefit assessment of the G-BA
Working group Section 35a	21 May 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	27 May 2019	Conduct of the oral hearing; commissioning of the medical consulting department with supplementary evaluation of documents
Working group Section 35a	5 June 2019 19 June 2019	Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the statement procedure
Subcommittee Medicinal products	25 June 2019	Concluding discussion of the proposed resolution
Plenum	4 July 2019	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 July 2019

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

Prof Hecken