Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL):

Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Bedaquiline (New Therapeutic Indication: pulmonary multidrug-resistant tuberculosis, 5 to 11 years)

of 16 September 2021

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. 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 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 (Sirturo) was listed for the first time on 15 May 2014 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 29 March 2021, Sirturo 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 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 December 2008, p. 7).

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) 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 and probability of the additional benefit 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 costs and patient numbers. The benefit assessment was published 1 July 2021 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 also held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G21-11) and the statements made in the written statements and oral hearing process, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has evaluated 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 bedaquiline.

[1] General Methods, version 6.0 from 05.11.2020. 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.

Therapeutic indication of the resolution (resolution of 16 September 2021):

Sirturo is used in paediatric patients **(aged 5 years to less than 12 years** and weighing at least 15 kg) as part of an appropriate combination therapy for multidrug-resistant pulmonary tuberculosis (MDR-TB) when an effective treatment regimen cannot be otherwise composed due to resistance or intolerance.

2.1.2 Extend of the additional benefit and significance of the evidence

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

Children (aged 5 years to less than 12 years and weighing at least 15 kg) with multidrug-resistant pulmonary tuberculosis when an effective treatment regimen cannot be otherwise composed due to resistance or intolerance with the exception of bedaquiline (as part of an appropriate combination therapy)

For bedaquiline, as part of an appropriate combination therapy, for children (aged 5 years to less than 12 years and weighing at least 15 kg) with multidrug-resistant pulmonary tuberculosis (MDR-TB) when an effective treatment regimen cannot be established other than with bedaquiline due to resistance or intolerance, there is a hint of non-quantifiable additional benefit because the scientific evidence base does not allow quantification.

Justification:
Results are available from study C211 (interim report, data cut-off 10.01.2019) for children (aged 5 years to under 12 years) with MDR-TB. This is a single-arm, open-label, multicentre, Phase II study to evaluate the pharmacokinetics, safety, tolerability and anti-mycobacterial efficacy of bedaquiline as part of a combination therapy (base therapy or background regimen, BR) in children and adolescents with confirmed or probable MDR-TB. Data for the present benefit assessment are available for cohort 2 (≥ 5 to < 12 years). Cohort 2 of the study included 17 subjects. 15 subjects received at least one dose of bedaquiline (referred to here by the pharmaceutical company as the ITT population). The mean age was 7 years. Patients in this sub-population (n=15) were treated with bedaquiline for a period of 24 weeks.
The primary endpoints collected in study C211 were data on pharmacokinetics, safety, and tolerability during 24 weeks of treatment with bedaquiline. In addition, the morbidity endpoints "absence of pathogens in the sputum" and "Clinical TB symptomatology subsiding" - assessed by medical investigators" were recorded.
As the present study C211 is an open-label and non-randomised study without a control arm, a high risk of bias at study and endpoint level is generally assumed.

As a basis for the present benefit assessment, the results of cohort 2 of study C211 at week 24 are shown below.

Mortality
There were no deaths in cohort 2 of the C211 study.

Morbidity

Clinical TB symptomatology subsiding
The medical investigators should assess the subsiding of TB symptomatology in accordance with a consensus statement. Although a third-party assessment of symptomatology is not *per se* patient-relevant, the subsiding of TB symptoms is a relevant aspect of a cure.
It was summarised at week 24 into "completely subsided," "partially subsided," and "not subsided," although it remains unclear how the categorisation was done. A standardised procedure with *a priori* defined criteria for classification was not provided in the multicentre study. The systematic assessment of the individual symptoms in the eCRFs was only included subsequently with Amendment 5 of the study protocol. Prior to this protocol change, symptoms were recorded according to the pharmaceutical company; however, baseline data are not available for all patients.
Due to the unclear operationalisation, the endpoint cannot be assessed.

Absence of pathogens in the sputum
In the C211 study, only subjects with confirmed MDR-TB and *Mycobacteria Growth Indicator Tube* (MGIT)-evaluable samples during the course of the study were assessed for the endpoint "Absence of pathogens in the sputum".
The operationalisation of the endpoint in the study required the demonstration of pathogen freedom by two consecutive negative microbiological sputum cultures at a minimum interval of 25 days. In the German S2k guideline for the treatment of tuberculosis, 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 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. Therefore, it is questionable to what extent the endpoint "time to the absence of pathogens" alone can provide information on the actual duration of patient isolation in the present operationalisation.
The endpoint absence of pathogens in the sputum cannot be assessed overall and is presented additionally due to uncertainties of patient relevance and the other limitations mentioned above.

Quality of life
Data on quality of life were not assessed in the C211 study.

Side effects
Adverse events (AEs) were assessed for both the 24-week treatment phase with bedaquiline + BR and the entire study duration (24-week treatment phase (bedaquiline + BR) + follow-up phase (BR only)) up to the 10.01.2019 data cut-off) with a median observation period of 61 weeks.
AEs of severity ≥ 3 occurred in approximately 53% of subjects and serious AEs in approximately 13%. AEs of special interest occurred in approximately 53% of subjects, including hepatotoxicity in approximately 20% and liver-related coagulation and bleeding disorders (prothrombin time prolonged) in approximately 33%. In approximately 20% of subjects, AEs led to discontinuation of bedaquiline therapy, and approximately 27% AEs led to discontinuation of at least one medicinal product of the base therapy.

Overall assessment

Mortality, morbidity and side effects results are available based on cohort 2 of the C211 study for bedaquiline as part of appropriate combination therapy for the treatment of children (aged 5 years to less than 12 years and weighing at least 15 kg) with multidrug-resistant pulmonary tuberculosis (MDR-TB) when an effective treatment regimen cannot be established other than with bedaquiline due to resistance or intolerance.

There were no deaths in the C211 study.

In the endpoint category morbidity, the endpoints "absence of pathogens in the sputum" and "subsiding of TB symptoms (assessed by medical investigators)" were recorded.

The endpoints cannot be assessed due to limitations regarding the operationalisation, the single-arm study design, the small number of cases and the short observation period of the presented data cut-off of 24 weeks for this therapeutic indication. 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.

In summary, no conclusions on the extent of additional benefit can be derived from the data on side effects.

Due to the lack of comparative data, the short duration of the study, and the high risk of bias in the single-arm study C211, the G-BA classifies the extent of the additional benefit for bedaquiline as not quantifiable on the basis of the based on the criteria in Section 5, paragraph 7 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), taking into account the severity of the disease, the written statements and the oral hearing. Therefore, a quantitative assessment of the extent of the effect and quantification of the additional benefit according to the categories "minor"," considerable", or "major" based on the data presented is not possible.

Significance of the evidence

There is a high risk of bias at the study level for the C211 study presented due to the single-arm, open-label study design. Furthermore, the significance of the results is limited due to the small number of cases, the small number of evaluable cases and the short observation period for this therapeutic indication. Due to the limitations on the available evidence, the result is a hint for a non-quantifiable additional benefit concerning the significance of the evidence.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient bedaquiline (Sirturo). Bedaquiline has a marketing authorisation as an orphan drug and was authorised under "special conditions".

The present assessment relates to the therapeutic indication "children (aged 5 years to less than 12 years and weighing at least 15 kg) with multidrug-resistant pulmonary tuberculosis when an effective treatment regimen cannot be otherwise composed due to resistance or intolerance except for bedaquiline (as part of an appropriate combination therapy)."

The benefit assessment is based on the single-arm, open-label, multicentre phase II study C211, in which children with confirmed or probable MDR-TB were treated with bedaquiline as part of combination therapy over a period of 24 weeks (cohort 2).

Data on mortality, morbidity and adverse events are available; data on quality of life were not collected. There were no deaths in the C211 study. In summary, no conclusions on the extent of additional benefit can be derived from the data on morbidity and side effects.

In summary, for bedaquiline as part of combination therapy for multidrug-resistant pulmonary tuberculosis in children aged 5 years to less than 12 years, a hint of non-quantifiable additional benefit is derived because the scientific data basis does not allow quantification.

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.

The resolution is based on the information from the dossier of the pharmaceutical company. Overall, the patient number of approx. 1 patient derived by the pharmaceutical company is subject to uncertainties but is considered to be a largely plausible order of magnitude.

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: 22 July 2021):

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 (Sirturo) be used under directly observed therapy (DOT).

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.

Children and adolescents weighing between 30 and 40 kg are expected to have a higher average exposure compared to adult patients. This could be associated with an increased risk of QT prolongation or hepatotoxicity.

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: 1 September 2021).

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 Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined based on consumption. The required number of packs of a particular potency was first determined based on consumption to calculate the annual treatment costs. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated based on the costs per pack after deduction of the statutory rebates.

The recommended dosage of Sirturo in children and adolescents (5 years to less than 12 years) depends on the body weight according to the product information. In weeks 1 to 2, bedaquiline is administered daily (160 mg, 200 mg and 400 mg, respectively). At weeks 3 to 24, bedaquiline is administered 3 times weekly (80 mg, 100 mg, and 200 mg, respectively).

The use of Sirturo is limited to 24 weeks.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Bedaquiline	Week 1 - 2: 1 x daily Week 3 - 24: 3 x weekly	Week 1 - 2: 14 Week 3 - 24: 66	1	80

Consumption:

Designation of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Bedaquiline	Week 1-2: 160 / 200 / 400 mg 1 x daily Week 3-24: 80 / 100 / 200 mg 3 x weekly	80 – 400 mg	Week 1 - 2 1 x 100 mg + 3 x 20 mg – 4 x 100 mg Week 3-24: 4 x 20 mg – 2 x 100 mg	Week 1 - 2 14 Week 3-24: 66	306 x 20 mg + 14 x 100 mg – 188 x 100 mg

Costs:

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					
Bedaquiline (20 mg)	60 TAB	€ 1,888.27	€ 1.77	€ 0.00	€ 1,886.50
Bedaquiline (100 mg)	24 TAB	€ 3,719.15	€ 1.77	€ 0.00	€ 3,717.38
Abbreviations: TAB = Tablets					

LAUER-TAXE® last revised: 1 September 2021

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 standard expenditure in the course of the treatment are not shown.

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

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 March 2021, 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, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 July 2021 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 22 July 2021.

The oral hearing was held on 10 August 2021.

An amendment to the benefit assessment with a supplementary assessment was submitted on 12 August 2021.

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 the 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 7 September 2021, and the draft resolution was approved.

At its session on 16 September 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Sub-committee Medicinal product	22 June 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	3 August 2021	Information on statements received; preparation of the oral hearing
Sub-committee Medicinal product	10 August 2021	Conduct of the oral hearing
Working group Section 35a	17 August 2021 31 August 2021	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
Sub-committee Medicinal product	7 September 2021	Final discussion of the draft resolution
Plenum	16 September 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 September 2021

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

Prof. Hecken