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
Maralixibat (Alagille syndrome, ≥ 2 months)

of 6 July 2023

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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient maralixibat on 15 January 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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, paragraph 1, number 1 VerfO on 13 January 2023.

Maralixibat indicated for the treatment of cholestatic pruritus in patients 2 months and older with Alagille syndrome (ALGS) is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the 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 17 April 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 evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G23-02) and the statements made in the written statement and oral hearing procedure, 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 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 maralixibat.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Maralixibat (Livmarli) in accordance with the product information

Livmarli is indicated for the treatment of cholestatic pruritus in patients with Alagille syndrome (ALGS) 2 months of age and older.

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

Therapeutic indication of the resolution (resolution of 6 July 2023):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

For children, adolescents and adults aged 2 months and older with cholestatic pruritus associated with Alagille syndrome, there is a hint for a non-quantifiable additional benefit because the scientific data basis does not allow quantification.

Justification:

For the assessment of the additional benefit, the pharmaceutical company submits the results of the label-enabling LUM001-304 (**ICONIC**) study as well as the **MRX-801** study. In addition, the **GALA-MRX-ALGS** study is presented as a supplement.

The **ICONIC** study is an open-label, long-term study including a double-blind, placebo-controlled, randomised withdrawal (RW) phase to investigate the safety and efficacy of maralixibat in children aged 12 months to 18 years with ALGS. A total of 31 patients with persistent itching (daily value > 2 in the ItchRO diary [maximum possible daily value = 4] for two consecutive weeks in the screening period) were enrolled in the study. All enrolled patients received maralixibat, initially in an open-label dose escalation phase (up to 400 µg/kg/day[2]) for 6 weeks, followed by a stable dose for 12 weeks. At week 19, patients were randomised to receive either maralixibat (n = 13) or placebo (n = 16) for 4 weeks (until week 22). This was followed by another open-label treatment phase for 26 weeks (until week 48) with stable doses of maralixibat up to 400 µg/kg/day. Afterwards, patients were given the option of a 52-week treatment extension, followed by long-term treatment. The primary endpoint was the change in fasting serum bile acids (sBA) level at week 22 versus week 18 in patients who had previously responded to maralixibat treatment. In addition, further endpoints on morbidity, health-related quality of life and side effects were assessed.

The **MRX-801** study is an open-label, uncontrolled phase II study to examine the safety and tolerability of maralixibat in the treatment of infants (< 12 months) with cholestatic liver disease (PFIC or ALGS). The study is divided into a 6-week dose escalation phase, a 7-week maintenance phase and a long-term phase (at least until the patients are 12 months old). Since only subjects with ALGS are relevant for this benefit assessment, only the ALGS cohort (n = 8) of the study is considered and presented below. As of the present interim data cut-off of 04.05.2022, the 13-week core study has already been completed by 7 children The median treatment duration is 137 days. The primary endpoint was the safety and tolerability of maralixibat. In addition, endpoints on the efficacy of maralixibat, but not on health-related quality of life, were also collected

The **GALA-MRX-ALGS** study is an investigation of long-term treatment with maralixibat in patients with ALGS compared to an external control cohort from the GALA study. For this purpose, an indirect comparison was carried out without a bridge comparator. Due to methodological limitations and the fact that more than 60% of the patients in the intervention group received maralixibat in a dosage that did not comply with the product information, the

[2] The dose of 400 µg/kg/day maralixibat chloride used corresponds to a dose of 380 µg/kg/day maralixibat as free base.

indirect comparison presented is not considered for the benefit assessment. In addition, the indirect comparison is also severely limited due to insufficient information on the comparability of patient characteristics (e.g. disease severity) and unavailable information on pruritus prevalence in the control cohort, and cannot be considered.

The results of the evaluable patient-relevant endpoints of the ICONIC and MRX-801 studies are discussed below. The comparator data from the randomised withdrawal phase of the ICONIC study are used for the present benefit assessment. The uncontrolled data at week 48 from the ICONIC study and the uncontrolled data from the MRX-801 study are presented additionally.

Mortality

Deaths were recorded in the ICONIC and MRX-801 studies as part of the safety assessment. There were no deaths in any of the two studies.

Morbidity

Pruritus by means of patient diary (ItchRO)

The endpoint of pruritus was assessed in the ICONIC and MRX-801 studies using the electronic patient diary Itch Reported Outcome (ItchRO), which was filled out in the morning and evening to record the severity grade of the itch during the night until waking or during the day using a 5-point Likert scale. The ItchRO was used in the ICONIC study in both a caregiver-reported (ItchRO(Obs)) and a patient-reported (ItchRO(Pt)) version. The ItchRO(Pt) was answered by all patients from the age of 9 or as early as 5 with the assistance of the caregiver, if necessary. The MRX-801 study used the ItchRO(Obs), but no results are available for the interim data cut-off presented.

The patient-reported recording of pruritus as a distressing symptom in the clinical picture of ALGS is considered to be patient-relevant. A parent or caregiver-reported assessment may also be considered patient-relevant for younger or cognitively impaired children who are unable to complete the questionnaire themselves.

While the mean values of the weekly averages of the morning assessment (nocturnal pruritus) at baseline were still balanced between the maralixibat and the placebo group, the assessment at week 18, time of randomisation and start of the RW phase showed a slightly lower value in the placebo arm. At week 22, the value in the placebo arm rose again almost to the baseline, while it remained at the low level in the maralixibat group. This difference is statistically significant.

Primarily, the responder analyses from the RW phase submitted subsequently in the context of the written statement procedure are used for the benefit assessment. There are evaluations of the percentage of subjects who achieved a weekly average score of ≤ 1 point (morning assessment, patient and caregiver-reported) at week 22, as well as evaluations of the percentage of days with a score ≤ 1 point (morning assessment, patient and caregiver-reported). In the latter, there is a statistically significant difference to the advantage of maralixibat.

In the continuous evaluations of the uncontrolled data over the entire course of the study, there is no renewed increase in pruritus until week 48.

However, there are still uncertainties regarding the validation of the survey instrument and there is no information on missing values.

With regard to the natural course of the disease, it should be noted that the affected patients suffer from severe pruritus, which is usually not well treatable. In clinical practice, pruritus may indicate liver transplantation. Against this background, in the present therapeutic indication of Alagille syndrome, the relief of pruritus has a significant clinical significance, which could not be achieved until now due to the insufficient treatment options.

Overall, the data presented can nevertheless only be interpreted with difficulty in terms of their significance, as they do not allow an assessment in comparison to the natural course of the disease in the present patient population. However, a relief of the itching in this therapeutic indication is to be basically considered as a therapeutic goal, since this represents the relevant severity of the Alagille syndrome.

Taken together, the administration of maralixibat presently shows a relevant reduction in pruritus in the RW phase compared to placebo, but the extent of which is non-quantifiable.

Pruritus using the clinical scratch scale

Based on observations during visits, clinical investigators in the ICONIC and MRX-801 studies also recorded itching in terms of scratching and visible damage to the skin due to scratching. The assessment was conducted using a clinical scratch scale ranging from 0 (= "no pruritus") to 5 (= "skin mutilation, bleeding and visible scarring").

The clinical scratch scale is thus another instrument with a different operationalisation for the assessment of pruritus or pruritus-associated symptoms.

The pharmaceutical company did not provide any information on the development or formal validation of the clinical scratch scale. The clinical scratch scale can therefore only be presented additionally.

Responder analyses assessing change in the RW phase of the ICONIC study are not available. The presented comparator analysis between maralixibat and placebo at week 22 relates to a change from baseline and not from week 18 (start of RW phase), and therefore cannot be used.

Change in pruritus by means of PIC/CIC

In the ICONIC study, the symptoms of itching and scratching were additionally assessed with a questionnaire on the impression of change *(Patient Impression of Change* (PIC) or *Caregiver Impression of Change* (CIC)). Each is a 7-point scale of perceived change in itch or itch-associated symptoms compared to itch prior to treatment start with the study medication. The PIC should be collected in all subjects ≥ 9 years of age; the CIC should be used in all study participants regardless of age.

The PIC/CIC is thus another instrument with a different operationalisation for recording the change in itch or itch-associated symptoms.

Since the assessment of the change by means of PIC/CIC was always carried out in comparison to baseline, no suitable data from the RW phase are available.

Fatigue

With the PedsQL-Fatigue, an additional module of the PedsQL (see quality of life) was used in the ICONIC study to record fatigue and fatigue-associated stress. Parent-reported versions of the instrument exist for subjects aged 2 years and older. In the case of children and adolescents aged 5 years and older, the instrument could additionally be collected in self-assessment, if necessary with the assistance of the caregiver. The reference period of the versions used was the past 4 weeks in each case.

PedsQL-Fatigue was evaluated using mean differences compared to baseline and week 18 for the RW phase. Responder analyses taking into account a response threshold of 15% of the scale range are not available. In the RW phase, there were no statistically significant differences between the treatment groups in the parent and child-reported versions.

Physical development

Anthropometric parameters can be assessed as patient-relevant morbidity parameters, especially in children with characteristic, disease-related growth disorders. Data adjusted for age and sex are preferred to absolute values.

In both studies, body height and body weight were collected as parameters of physical development during a physical examination at each visit, and standardised according to age and sex. For infants under 24 months of age, the WHO growth curves were used to derive the z scores, and from 24 months of age, the growth curves of the Center for Disease Control and Prevention (CDC) were used. However, no results on physical development for the interim data cut-off are available for the MRX-801 study.

For the ICONIC study, an evaluation of mean differences compared to baseline was carried out. All anthropometric parameters for recording physical development showed clearly negative deviations from the norm at the start of the study. Evaluations of a change in physical development in the RW phase (week 22 compared to week 18) are not available.

Anthropometric parameters on physical development are in principle patient-relevant in children and adolescents with Alagille syndrome, but the endpoint cannot be conclusively assessed on the basis of the methodological limitations in the present evaluation of the single-arm data.

Reduction of serum bile acid concentration

In the present therapeutic indication, the serum bile acid concentration is a clinically relevant parameter which is used for diagnosis and therapy management.

No valid data could be identified to show what effect a specific change in serum bile acid (sBA) concentration has on cholestatic pruritus. The sBA level is therefore classified as non-patient-relevant.

The primary endpoint of the ICONIC study (mean change in fasting sBA level at week 22 compared to week 18 in subjects who had previously responded to maralixibat treatment) is presented additionally in the benefit assessment. Since the primary endpoint only represents data for a sub-population of the ICONIC study, the s-BA level for the entire study population is also presented additionally.

This shows a statistically significant difference to the advantage of maralixibat.

<u>Quality of life</u>

Paediatric Quality of Life Inventory (PedsQL)

The PedsQL 4.0 measures the general health-related quality of life in children and adolescents. It consists of four multidimensional scales (Physical Functioning, Emotional functioning, Social functioning, and School functioning) with a total of 23 items and three sum scores: Total score, physical health summary score, psychosocial health summary score. The questionnaire consists of a Likert scale from 1 to 4 (1 = best function [never] to 4 = worst function [always]). The scores are then transformed into a scale of 1 to 100; higher scores indicate a higher quality of life.

The PedsQL is an established and adequately validated generic instrument for assessing the quality of life in pediatric populations with chronic conditions.

In the ICONIC study, different versions of the PedsQL core module were used to assess health-related quality of life, depending on the age of the test subject: Patient and parent reports for the core modules 5-7 year olds, 8-12 year olds and 13-18 year olds as well as a core module for parent reports for infants in a version for 1-12 months, 13-24 months and 2-4 years respectively.

The PedsQL was evaluated using mean differences compared to baseline and to week 18 for the RW phase. There were no statistically significant differences between the treatment arms; neither in the parent nor in the child-reported version.

Side effects

The pharmaceutical company shall submit evaluations of all AEs in the different study phases. According to SAP, only the newly occurring or worsening AEs were recorded in a study phase. It follows that the AE results of the RW phase are not meaningful as they do not include AEs that already occurred in the 18 preceding treatment weeks. In this respect, a risk of bias to the advantage of the maralixibat arm is to be expected since any improvement/reduction or absence of side effects in the placebo arm is not recorded. Therefore, only the non-comparator results of the single-arm treatment phases are used for the ICONIC study. The aggregated results for all AEs, which occurred in the treatment with maralixibat ≤ 400 µg/kg/day and were subsequently submitted in the context of the written statement procedure, are relevant for the benefit assessment.

It remains unclear whether it was possible to distinguish sufficiently between symptoms of the underlying disease and side effects on the basis of the provisions in the protocol. However, considering the available safety data in the RW phase, it can be assumed that symptomatology was also rated as AE.

For the MRX-801 study, all AEs that occurred in the treatment with maralixibat are shown, both during the up-titration and the maintenance phase.

In view of the limitations of the study design presented, the small sample size and the limitations in the collection and evaluation of the safety data with regard to the recording of disease symptomatology, a conclusive assessment of the safety of maralixibat in children and adolescents with ALGS is not possible.

Overall assessment

For the benefit assessment of maralixibat for the treatment of cholestatic pruritus in adults, adolescents and children 2 months of age and older with Alagille syndrome (ALGS), results from the uncontrolled ICONIC study on mortality, morbidity, health-related quality of life and side effects are available. In addition, comparator data versus placebo are available from the four-week randomised withdrawal phase (RW phase) of the ICONIC study on the endpoint categories of morbidity and health-related quality of life. For the uncontrolled MRX-801 study, which investigates infants aged < 12 months, results on mortality and side effects were presented. The indirect comparison GALA-MRX-ALGS cannot be used for the benefit assessment because more than 60% of the patients in the intervention group received maralixibat in a dosage that did not comply with the product information. The comparator data from the randomised withdrawal phase of the ICONIC study are used for the present benefit assessment. However, the comparator RW phase is altogether too short to be able to derive statements on the quantification of the additional benefit.

In both the ICONIC and the MRX-801 studies, no deaths occurred until the respective data cut-offs considered.

In the endpoint category of morbidity, the endpoint of pruritus of the ICONIC study is used for the present benefit assessment. For the endpoint of pruritus, the RW phase shows a statistically significant advantage of maralixibat over placebo in the operationalisation "percentage of days with a value ≤ 1 point" in both the caregiver-reported and patient-reported ItchRO. Due to the natural course of Alagille syndrome, which is associated with severe, persistent and hardly treatable pruritus, itch relief is of significant clinical importance in the present therapeutic indication.

Health-related quality of life was assessed in the ICONIC study with a measurement instrument suitable for the paediatric patient population. There are no statistically significant differences during the RW phase. Due to the study design, no conclusive assessment can be made.

With regard to the results on side effects, severe (CTCAE grade 3 or 4) and serious adverse events as well as therapy discontinuation due to adverse events occurred in part during treatment with maralixibat. A conclusive assessment of the safety of maralixibat in children and adolescents with ALGS is not possible given the study design presented.

In the overall assessment, the administration of maralixibat shows a relevant reduction in pruritus, but the extent of this reduction is non-quantifiable. In particular, as the study design presented is not considered sufficient to make a conclusive assessment of patient-relevant endpoints other than the result on pruritus, a non-quantifiable additional benefit is determined in the overall assessment of the available results for maralixibat for the treatment of cholestatic pruritus in adults, adolescents and children aged 2 months and older with ALGS, because the scientific data basis does not allow quantification.

Significance of the evidence

The ICONIC study provides comparator data from the four-week RW phase and single-arm data from the entire study population for change from baseline. The uncontrolled results are fundamentally associated with a high risk of bias. The risk of bias for the RW phase is also estimated to be high due to the lack of a washout period, expected carry-over effects and the short comparator study duration of 4 weeks.

The MRX-801 study is a single-arm study so that a comparator assessment is not possible.

In the overall review the result is a hint for an additional benefit with regard to significance of the evidence.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of the new medicinal product Livmarli® with the active ingredient maralixibat, which was approved as an orphan drug under special conditions for the treatment of cholestatic pruritus in patients aged 2 months and older with Alagille syndrome.

For adults, adolescents and children aged 2 months and older with cholestatic pruritus associated with Alagille syndrome, the pharmaceutical company presents results of the 4-week randomised withdrawal phase (RW phase) of the ICONIC study as well as uncontrolled baseline comparisons of the ICONIC and MRX-801 studies. The comparator data from the RW phase of the ICONIC study are used here. However, the RW phase is altogether too short to be able to derive statements on the quantification of the additional benefit.

There were no deaths in both studies.

In the category of morbidity, a relevant reduction in pruritus was observed as assessed by ItchRO(Obs) and ItchRO(Pt). Due to the natural course of the disease, which is accompanied by severe, persistent and hardly treatable pruritus, itch relief has a significant clinical significance in the present therapeutic indication.

There were no statistically significant differences in the health-related quality of life. Due to the study design, no conclusive assessment can be made.

The side effects cannot be conclusively assessed, given the study design presented and due to the small sample size and the recording of disease symptomatology.

The significance of the evidence is classified in the hint category since uncertainties arise both from the absence of a comparator arm and from carry-over effects during the RW phase.

In the overall assessment, given the present study design, a hint for a non-quantifiable additional benefit of maralixibat is identified 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 (SHI).

The resolution is based on the information from the dossier assessment of the IQWiG (mandate G23-02).

The G-BA takes into account the patient numbers, which are stated in the pharmaceutical company's dossier, but are subject to uncertainties. Based on the limited epidemiological data basis on incidence per live birth in the therapeutic indication, the lower limit set tends to be underestimated and the upper limit is not comprehensible. In addition, there are uncertainties due to a probably overestimated percentage of patients with cholestatic pruritus and the mathematically incomprehensible deduction of prevalent patients aged less than 2 months. Overall, these uncertainties do not allow an assessment of the extent to which an underestimation or overestimation of the patient numbers can be assumed.

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 Livmarli (active ingredient: maralixibat) at the following publicly accessible link (last access: 12 April 2023):

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

Treatment with maralixibat should only be initiated and monitored by doctors experienced in treating cholestatic liver diseases.

This medicinal product was approved under “special conditions”. This means that due to the rarity of the disease, it was not possible to obtain complete information on this medicinal product. The European Medicines Agency will assess any new information that becomes available on an annual basis, and, if necessary, the summary of product characteristics will be updated.

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 2023).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments, e.g. because of side effects or comorbidities, are not taken into account when calculating the annual treatment costs.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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				
Maralixibat	Continuously, 1 x daily	365	1	365

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					
Maralixibat (380 µg/kg/day)	5 - 6 kg 1,900 µg	1,900 µg	0.2 ml	365	73 ml
	> 70 kg 28,500 µg	28,500 µg	3 ml	365	1,095 ml

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					
Maralixibat	30	€ 45,218.54	€ 2.00	€ 4,421.40	€ 40,795.14

LAUER-TAXE® last revised: 15 June 2023

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 Maralixibat

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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 13 January 2023, the pharmaceutical company submitted a dossier for the benefit assessment of maralixibat to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 17 April 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 8 May 2023.

The oral hearing was held on 22 May 2023.

An amendment to the benefit assessment with a supplementary assessment was submitted on 12 June 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 27 June 2023, and the proposed resolution was approved.

At its session on 6 July 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	27 June 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	10 May 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	22 May 2023	Conduct of the oral hearing
Working group Section 35a	31 May 2023 21 June 2023	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	27 June 2023	Concluding discussion of the draft resolution
Plenum	6 July 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 July 2023

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

Prof. Hecken