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 (new therapeutic indication: progressive familial intrahepatic cholestasis (PFIC), ≥ 3 months)

of 6 February 2025

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 all 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 SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation. 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 active ingredient maralixibat (Livmarli) was listed for the first time on 15 January 2023 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 28 June 2024, maralixibat 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, 12.12.2008, sentence 7).

On 26 July 2024, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient maralixibat with the new therapeutic indication "Livmarli is indicated for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients 3 months of age and older“ in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

Maralixibat indicated for the treatment of progressive familial intrahepatic cholestasis 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 1 November 2024 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 G21-25) 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 marketing authorisation 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 progressive familial intrahepatic cholestasis (PFIC) in patients 3 months of age and older.

Therapeutic indication of the resolution (resolution of 6 February 2025):

See therapeutic indication according to marketing authorisation.

2.1.2 Extent of the additional benefit and significance of the evidence

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

Adults, adolescents and children 3 months of age and older with progressive familial intrahepatic cholestasis

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

Justification:

For the benefit assessment, the pharmaceutical company presented analyses of the MRX-502 (MARCH-PFIC) approval study and the ongoing MRX-801 (RISE) study.

MARCH-PFIC study

The MARCH-PFIC study is a multinational, randomised, double-blind, phase III study investigating maralixibat versus placebo in patients with PFIC 12 months to < 18 years of age. Randomisation was carried out in a 1:1 ratio to maralixibat or placebo, stratified according to two defined cohorts:

a) Primary cohort: Subjects with a biallelic homozygous disease-causing variant in PFIC2, except subjects with t-PFIC2, low or fluctuating serum bile acid levels or previous surgery to treat PFIC.

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

b) Supplementary cohort: Includes all other study participants. In this cohort, stratification was performed prior to randomisation according to PFIC1, PFIC3 and all other study participants in the cohort. The group of all other study participants here includes subjects with t-PFIC2, PFIC4, subjects with PFIC phenotype without known mutation, heterozygosity with other known mutations or with intermittent cholestasis manifested by fluctuating sBA level as well as subjects with PFIC after internal or external bile duct surgery or in whom the surgery was cancelled.

The study comprises a 6-week screening phase, a 26-week treatment phase including a 4-6-week dose escalation phase and a 1-week follow-up phase. Maralixibat was dosed as follows: Week 1: 150 µg/kg twice daily (BID), week 2: 300 µg/kg BID, week 3: 450 µg/kg BID, week 4: 600 µg/kg BID, week 4 to 26: 600 µg/kg BID. Following an up-titration phase, the study participants received a final dose of 600 µg/kg maralixibat twice daily. However, for children under 5 years of age, this dosage does not correspond to the requirements in the product information, which recommends a maximum dose of 285 µg/kg twice daily for this patient population.

For the MARCH-PFIC study, the data of the final data cut-off from 14 October 2022 are available.

At the end of the 26-week double-blind treatment phase, patients had the opportunity to take part in an extension study (MRX-503 study).

The pharmaceutical company formed 3 patient populations for the evaluation of the study: The primary population comprises all subjects in the primary cohort (nt-PFIC2). The PFIC population includes participants with the biallelic disease-causing variants PFIC1, nt-PFIC2, PFIC3, PFIC4 and PFIC6. This population excludes subjects with low or fluctuating sBA or previous surgery to treat PFIC. All study participants are included in the total population.

The primary population restricted to nt-PFIC2 and the PFIC population (participants with biallelic disease-causing variants) represent only a part of the underlying therapeutic indication and are not considered further in the benefit assessment. Due to the therapeutic indication, which includes all disease-causing mutations of progressive familial intrahepatic cholestasis, the data of the total population are used to derive the additional benefit.

As part of the written statement procedure, the pharmaceutical company also presented evaluations of the interim data cut-off from 28 June 2023 for the ongoing MRX-801 (RISE) study.

<u>RISE study (presented additionally)</u>

The RISE study is an open-label, multicentre, uncontrolled phase II study investigating maralixibat in infants < 12 months of age with cholestatic liver diseases (PFIC or Alagille syndrome).

The study comprises a screening phase of up to 4 weeks, followed by 1-6 weeks of dose escalation and a 7-week maintenance phase. After completion of the maintenance phase, the infants enter a long-term phase up to a minimum age of 12 months. After crossing the age of 12 months, the infants remain in the long-term phase of the study.

Since only subjects with PFIC are relevant for this benefit assessment, only the PFIC cohort (n = 10) of the study is considered below.

The results of the evaluable patient-relevant endpoints of the MARCH-PFIC and RISE studies are discussed below. The comparator data from the MARCH-PFIC study were used for this benefit assessment. The uncontrolled data from the RISE study are only presented additionally.

MARCH-PFIC

Mortality

No deaths occurred in the study.

Morbidity

Pruritus using patient diary (ItchRO)

The pruritus endpoint was assessed using the electronic patient diary "Itch Reported Outcome" (ItchRO). This was used in both a caregiver-reported (ItchRO(Obs)) and a patient-reported (ItchRO(Pt)) version. The ItchRO(Pt) was completed by all patients 9 years and older (age at screening visit); children under the age of 9 years did not complete the ItchRO(Pt).

The return rate for the ItchRO(Pt) was too low, which is why only the results of the ItchRO(Obs) can be considered in the benefit assessment.

For this purpose, the respective caregiver was asked daily in the morning about the severity of itch-associated symptoms such as rubbing, scratching, skin injuries, sleep disorders or irritability at night. Based on this, a summarised classification of the pruritus should be made. In addition, the caregiver should give an estimate of how much time the child has spent scratching or rubbing.

The child was also surveyed in the evening, except that the time from waking up to going to bed was asked.

In the dossier, analyses of the percentage of ItchRO(Obs) responders at week 15-26 as well as analyses of the mean change in severity of ItchRO(Obs) at week 15-26 compared to baseline were presented. Responders were defined as the percentage of subjects with an improvement ≥ 1 point or severity score ≤ 1. For the analyses of the mean change in severity of ItchRO(Obs) at week 15-26 compared to baseline, the data from the survey of morning and evening ItchRO(Obs) and the average highest daily ItchRO severity were used.

The results of the responder analysis are used for the present assessment. Based on this operationalisation, there was a statistically significant advantage in favour of maralixibat over placebo for the endpoint of pruritus.

Physical development

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

For the endpoint of physical development, the parameters of body height and body weight were collected as part of a physical examination at each visit and standardised according to age and sex. For this purpose, the growth curves of the World Health Organisation were used to derive the z scores for infants under 24 months and the growth curves of the Centers for Disease Control and Prevention for children aged 24 months and older.

In the total population of the MARCH-PFIC study, the analyses at week 18-26 showed a statistically significant advantage of maralixibat over placebo compared to baseline for both body height and body weight.

Both studies showed significant negative deviations from the standard values for body height and body weight. While both endpoints in the intervention arm showed improvements in the z score compared to baseline, these remained almost unchanged in the placebo arm. During the oral hearing, the participating clinicians confirmed that growth disturbances frequently occur in children with PFIC. At the same time, the clinical relevance of improving the z score was emphasised. The change in body weight is more pronounced in the MARCH-PFIC study and is assessed by the G-BA as a clinically relevant improvement. The effect on body height is less pronounced than for body weight, so that the period for a comparative assessment from week 18 to 26 compared to baseline is too short to conclusively assess the clinical relevance of the changes in body height.

Reduction of serum bile acid concentration

The fasting values of serum bile acid (sBA) were collected as part of a blood sample by the study personnel as a cholestasis biomarker in the MARCH-PFIC study at every study visit, except visit 3. The mean change in the total sBA level between baseline and the average of weeks 18, 22 and 26 was analysed.

For the change in sBA level between baseline and the average of weeks 18 - 26, there was a statistically relevant advantage of treatment with maralixibat compared to placebo.

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

The reduction of bile acids is considered a therapy goal in order to reduce the risk of secondary damage to the liver. The increased serum bile acid concentration is a direct manifestation of PFIC and, as a disease toxin, is causative for the disease symptomatology. However, the symptomatology of patients with PFIC is different from patient to patient.

No valid data could be identified to show what effect a specific change in serum bile acid concentration has on patient-individual symptomatology or on the risk of liver damage. The sBA level is therefore not classified as patient-relevant per se.

Furthermore, it is even more difficult to interpret the results since the dosage of maralixibat used in the study did not correspond to the requirements in the product information for the majority of the patients enrolled.

The endpoint "reduction in serum bile acid concentration" is therefore not considered in the benefit assessment.

Fatigue

With the PedsQL – Multidimensional Fatigue Scale (parent-reported for children older than 2 years and self-reported for children and adolescents older than 8 years), an additional module of the PedsQL (see quality of life) was used in the MARCH-PFIC study to assess fatigue and fatigue-associated stress.

For the self-reported version of the PedsQL-Fatigue, the return rates in the intervention arm were below 70%, which is why the results are not used.

The parent-reported version of the PedsQL-Fatigue only exists for children older than 2 years, whereas children older than 1 year could be enrolled in the MARCH-PFIC study. In conjunction with the distribution data for the age of the children, it seems likely that the return rate for the PedsQL for the sub-population of children ≥ 2 years is above 70%. The results of the PedsQL-Fatigue are therefore used for this assessment. As no responder analyses are available, the mean changes compared to baseline are used.

For the endpoint of fatigue, the change in PedsQL-Fatigue (parent-reported) at week 18-26 compared to baseline showed a statistically significant advantage of maralixibat over placebo. The confidence interval of the Hedge'g is also completely above the threshold value of 0.2.

Quality of life

Paediatric Quality of Life Inventory (PedsQL)

The PedsQL 3.0 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 summary scores: Total score, physical health summary score, psychosocial health summary score. The questionnaire consists of a Likert scale from 1 to 4. 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.

For the total population of the MARCH-PFIC study, only the results of the parent-reported version of the PedsQL are taken into account, as the return rate for the self-reported version of the PedsQL (from the age of 8 years) in the intervention arm is below 70%.

Based on the parent-reported version of the PedsQL, there were no statistically significant differences between the treatment arms.

Side effects

The safety results in the total population of the MARCH-PFIC study showed no statistically significant differences between the treatment groups in terms of SAEs and severe AEs or therapy discontinuation due to AEs. In detail, there was a statistically significant disadvantage of maralixibat compared to placebo for the event of diarrhoea (AE of special interest).

RISE study (presented additionally)

Mortality

No deaths occurred in the study.

Morbidity

Pruritus using the clinical scratch scale (presented additionally)

Based on observations during visits, clinical investigators recorded itching in terms of scratching and visible damage to the skin due to scratching as part of the study. The assessment was conducted using a clinical scratch scale ranging from 0 (= "no pruritus") to 4 (= "skin mutilation, bleeding and visible scarring"). If possible, the same subject should carry out the assessments for a subject's visits.

The clinical scratch scale shows a slight deterioration in pruritus at week 13 from baseline. When interpreting the results, however, it must be taken into account that the patient population of the study is very young and that cholestatic pruritus in infants only develops during motor development in the first year of life, in addition to the non-comparative data basis.

Physical development

The endpoint of physical development showed an almost unchanged growth deficit for the infants in terms of body height (z-scores). There were slight numerical improvements in body weight (z score) at week 13. However, the study duration of the core phase of 13 weeks is not sufficient to be able to assess the effects on physical development.

Quality of life

No data on health-related quality of life are available.

Side effects

All infants experienced at least 1 AE in the core study phase, 3 infants experienced at least 1 SAE, 1 infant experienced a severe AE and 1 infant discontinued the study due to AE. Overall, the very young patient population of the RISE study showed a safety profile of maralixibat that was comparable to that of the MARCH-PFIC study, although the data are limited by the small patient number, the short duration of observation and the single-arm study design.

Overall assessment

For the benefit assessment of maralixibat for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients aged 3 months and older, results of the randomised, double-blind MARCH-PFIC study comparing maralixibat with placebo are available. Children older than 12 months and adolescents up to 18 years with PFIC were enrolled. Most study participants received (after an up-titration phase) a final dose of 600 µg/kg maralixibat twice daily. For children under 5 years of age, this dosage does not correspond to the requirements in the product information, which recommends a maximum dose of 285 µg/kg twice daily for this patient population.

The treatment of maralixibat in infants < 12 months with PFIC was investigated in the uncontrolled RISE study (n = 10). Due to the small number of patients and the lack of comparison, the results of the single-arm RISE study are only presented additionally. The assessment of the additional benefit is therefore based on the comparator data from the MARCH-PFIC study.

No deaths occurred in the MARCH-PFIC study.

In the morbidity category, there was a statistically significant advantage in favour of maralixibat over placebo for the endpoint of pruritus, assessed using ItchRO(Obs), and for the endpoint of fatigue, assessed using PedsQL-Fatigue. Furthermore, there was a statistically significant advantage of maralixibat over placebo for both body height (z score) and body weight (z score) for the endpoint of physical development. The difference in body weight is considered clinically relevant.

There were no statistically significant differences between the treatment arms for the category of health-related quality of life, assessed using PedsQL, or for the category of side effects. In detail, there was a statistically significant disadvantage of maralixibat compared to placebo for the event of diarrhoea (AE of special interest).

The positive effects in the endpoints of pruritus, fatigue and physical development (body weight) are therefore not offset by any negative effects. However, when assessing the results, it should be noted that the majority of patients in the MARCH-PFIC study received a dosage of 600 µg/kg maralixibat twice daily. Although the MARCH-PFIC study included participants up to the age of 18 years, the majority of patients were younger than 6 years. In the total population, the median age was 3 years in the intervention group and 3.6 years in the control group. For children under 5 years of age, the product information recommends a maximum permitted dose of 285 µg/kg maralixibat twice daily. The dosage of maralixibat used in the study therefore does not correspond to the requirements in the product information for the majority of the patients enrolled.

Due to the excessive dosage of maralixibat in children under 5 years of age in the MARCH-PFIC study, the transferability of the study results to the German healthcare context must be questioned. The overall extent of the advantages shown in the morbidity endpoint category can therefore not be quantified.

In addition, no comparator data are available for the patient population of infants aged 3 to < 12 months, which is also covered by the marketing authorisation.

In the overall assessment of the available results on the patient-relevant endpoints, the G-BA therefore classifies the extent of the additional benefit of maralixibat for the treatment of progressive familial intrahepatic cholestasis in adults, adolescents and children aged 3 months and older on the basis of the criteria in Section 5, paragraph 8 in conjunction with Section 5, paragraph 7, sentence 1, numbers 1 to 4 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as non-quantifiable because the scientific data basis does not allow quantification.

Significance of the evidence

The present benefit assessment is based on evaluations of the MARCH-PFIC RCT.

The risk of bias for the MARCH-PFIC study is classified as low. However, at the endpoint level, there is a high risk of bias for the endpoints of physical development, PedsQL-Fatigue and PedsQL.

The high risk of bias of the endpoint of physical development is due to differences between the treatment arms at baseline, especially for the z score of body weight, with greater deviations from the standard documented for subjects in the maralixibat arm than for participants in the placebo arm. In addition, no results are available in the underlying natural units (e.g. kg or cm).

For the PedsQL-Fatigue endpoint, there are only parent-reported versions of the questionnaire for children aged 2 years and older. For this reason, results of the PedsQL-Fatigue are only available for this sub-population of the MARCH-PFIC study. It is not clear from the available study documents how many children in the MARCH-PFIC study were younger than 2 years and were therefore ineligible for the PedsQL-Fatigue survey. In conjunction with the distribution data for age at baseline, it seems likely that the return rate for the PedsQL-Fatigue for the sub-population of patients ≥ 2 years is above 70%. A clear calculation of the return rates for the parent-reported version of the PedsQL-Fatigue endpoint is therefore not possible and the risk of bias is classified as high.

For the PedsQL endpoint, the return rate in the maralixibat arm is already only 87% at baseline and falls further to 83% for the change at week 18-26. In the placebo-arm, the return rate for the change from baseline to week 18-26 was 87%. Therefore, the risk of bias for this endpoint is also classified as high.

Due to these uncertainties, the overall reliability of data is classified as a hint.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient maralixibat. The medicinal product Livmarli was approved under "exceptional circumstances" as an orphan drug for the treatment of progressive familial intrahepatic cholestasis (PFIC) in patients 3 months and older.

The results of the randomised, double-blind, placebo-controlled phase III MARCH-PFIC study for patients with PFIC 12 months and older are available for the benefit assessment. The pharmaceutical company also presented the interim results of the single-arm RISE study investigating children aged 3 to 12 months. However, these are only presented additionally in the benefit assessment.

No deaths occurred in the MARCH-PFIC study used to assess the additional benefit. In the morbidity category, statistically significant advantages were shown in the endpoints of pruritus, physical development (body weight) and fatigue. No statistically significant differences were observed between the treatment arms in the categories of quality of life and side effects.

Overall, the positive effects shown are therefore not offset by any negative effects.

However, the transferability of the study results to the German healthcare context must be questioned due to the non-compliant dosing of maralixibat in children under 5 years of age in

the MARCH-PFIC study. The overall extent of the advantages shown in the morbidity endpoint category can therefore not be quantified. In the overall assessment, a non-quantifiable additional benefit is therefore identified since 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 data on patient numbers given in the IQWiG assessment [G24-19].

The pharmaceutical company's data on the number of patients in the SHI target population are uncertain and underestimated in the overall assessment. This results from an underestimated average survival time and thus prevalence of PFIC.

In the benefit assessment of the active ingredient odevixibat in the comparable therapeutic indication, a significantly lower number of approx. 40 to 110 patients was used in the SHI target population. This can be explained by a more differentiated approach to deriving the prevalence, depending on the genetic subtypes of PFIC in the current benefit assessment.

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: 28 January 2025):

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 “exceptional circumstances”. 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.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material contains, in particular, information and warnings on medication errors due to wrong dosage.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 January 2025).

Treatment period:

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.

The active ingredient maralixibat is administered according to body weight. For dosages depending on body weight, the average body measurements from the "German Health Interview and Examination Survey for Children and Adolescents (KiGGS)"[2] were applied (average body weight of a 3-month-old child: 5.87 kg), for children 5 years of age and above, the average body measurements from the official representative statistics "Microcensus 2017 - Body measurements of the population"[3] were applied (average body weight of a child up to 5 years of age: 18.8 kg, average body weight of a child older than 5 years: 20.8 kg) and for adults from the "Microcensus 2021 – Body measurements of the population"[4] were applied (average body weight 77.7 kg).

The maximum recommended dose of Livmarli in PFIC patients under 5 years of age is 285 µg/kg twice daily due to the propylene glycol content. Due to this limitation, two populations (children ≥ 3 months to < 5 years; children ≥ 5 years and adults) were formed when calculating the costs and consumption.

For patients over 50 kg, there was also a deviation from the weight-dependent dosage. According to the product information, the maximum daily dose is 57 mg maralixibat.

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 – 2 x daily	365 - 730	1	365

[2] Contributions to Federal Health Reporting. Reference percentiles for anthropometric measures and blood pressure from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS) (2013, both sexes, from birth), https://edoc.rki.de/handle/176904/3254

[3] Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

[4] Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Consumption:

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

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

According to the requirements in the product information, the medicinal product must be used within 130 days of opening the bottle. Due to the weight-dependent dosage, some patients therefore discard the bottle prematurely, resulting in an average annual consumption depending on the maximum shelf life after the bottle has been opened.

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 (Children ≥ 3 months to < 5 years)	1 -2 x daily 285 µg/kg each 1.67 mg – 10.72 mg	1.67 mg – 10.72 mg	1.67 mg = 0.15 ml - 10.72 mg = 1 ml	365.0	54.8 ml – 365 ml
Maralixibat (Children ≥ 5 years and adults)	1 x daily 285 µg/kg each – 2 x daily 570 µg/kg each 5.93 mg – 57.0 mg	5.93 mg – 57.0 mg	5.93 mg = 0.6 ml – 57.0 mg = 6 ml	365.0	219 ml – 2190 ml

Costs:

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

Costs of the medicinal products:

Designation of the therapy	Packaging size	Cost (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 (9.5 mg/ml)	30 OS	€ 29,402.33	€ 2.00	€ 1,675.88	€ 27,724.45
Abbreviations: OS = oral solution					

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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 Designation of 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 the assessed medicinal product

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

Basic principles of the assessed medicinal product

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

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered

due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

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

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

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

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

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

Concomitant active ingredient

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

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

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

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

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

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

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

Designation

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

combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

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

Exception to the designation

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

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

Legal effects of the designation

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

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adults, adolescents and children 3 months of age and older with progressive familial intrahepatic cholestasis

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for maralixibat (Livmarli); Livmarli 9.5 mg/ml oral solution; last revised: June 2024

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 26 July 2024, 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 2 VerfO.

The benefit assessment of the G-BA was published on 1 November 2024 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 22 November 2024.

The oral hearing was held on 9 December 2024.

An amendment to the benefit assessment with a supplementary assessment was submitted on 10 January 2025.

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 28 January 2025, and the draft resolution was approved.

At its session on 6 February 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	29 October 2024	Information of the benefit assessment of the G-BA
Working group Section 35a	4 December 2024	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 December 2024	Conduct of the oral hearing
Working group Section 35a	18 December 2024 15 January 2025	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	28 January 2025	Concluding discussion of the draft resolution
Plenum	6 February 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 6 February 2025

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

Prof. Hecken