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 Elafibranor (primary biliary cholangitis)

of 3 April 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 their 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 their 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 elafibranor on 15 October 2024 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 14 October 2024.

Elafibranor for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA 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 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 assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 January 2025 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 pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G24-30) and the statements made in the written statement and oral hearing procedure, as well as the amendment to the benefit assessment drawn up by the G-BA.

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 elafibranor.

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

## 2.1 Additional benefit of the medicinal product

### 2.1.1 Approved therapeutic indication of Elafibranor (Iqirvo) in accordance with the product information

Iqirvo is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA.

**Therapeutic indication of the resolution (resolution of 3 April 2025):**

See the approved therapeutic indication.

### 2.1.2 Extent of the additional benefit and significance of the evidence

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

For adults with primary biliary cholangitis (PBC) and inadequate response or intolerance to ursodeoxycholic acid (UDCA), there is a hint for a minor additional benefit of elafibranor.

Justification:

For the benefit assessment, the pharmaceutical company submitted the data from the label-enabling ELATIVE study.

The ELATIVE study is a multicentre, randomised, double-blind, placebo-controlled phase III study investigating the efficacy, safety and tolerability of elafibranor in patients with PBC with inadequate response or intolerance to UDCA. A total of 161 adults aged 18 to 75 years with a proven diagnosis of PBC and UDCA treatment for at least 12 months or UDCA intolerance were enrolled; 108 subjects in the intervention arm and 53 subjects in the control arm. The screening phase was followed by a double-blind phase (DB phase) of at least 52 weeks with a possible prolongation of a further 52 weeks and a 4 to 5-year long-term extension phase (LTE phase). The primary endpoint of the study was biochemical response to the treatment at week 52. In addition, other endpoints in the categories of mortality, morbidity, health-related quality of life and side effects were assessed.

As part of the written statement procedure, the pharmaceutical company subsequently submitted results of post-hoc responder analyses with a response threshold of an improvement or deterioration by at least 15% at week 52 of the ELATIVE study. For the benefit assessment, the responder analyses of an improvement by at least 15% are used.

No patients in a severely extensive-stage of primary biliary cholangitis were examined in the ELATIVE study. In addition, only a few of the patients enrolled in the study received monotherapy with elafibranor. However, both patient groups are covered by the marketing authorisation of elafibranor.

<u>Mortality</u>

Deaths from any cause were collected as part of the safety assessment. Two deaths occurred with elafibranor in the study. There was no statistically significant difference between the study arms.

Morbidity

*Biochemical response*

The composite endpoint of biochemical response at week 52 versus baseline was the primary endpoint of the ELATIVE study. It comprises the response of the laboratory parameters alkaline phosphatase (ALP) and total bilirubin (TB) (ALP < 1.67 × ULN and TB ≤ ULN and ALP reduction ≥ 15%).

The endpoint of biochemical response showed a statistically significant advantage of elafibranor over placebo.

The collection of laboratory parameters is not directly patient-relevant. Furthermore, no valid data could be identified to show what effects a specific change in the laboratory parameters included in the composite endpoint has on patient-individual symptomatology, mortality or the risk of liver damage.

The endpoint of biochemical response is therefore not used for the present benefit assessment and is only presented additionally.

*Clinical events*

The composite endpoint of clinical events comprises the subcomponents of liver transplantation, uncontrolled ascites requiring treatment and hospitalisations due to variceal haemorrhage, hepatic encephalopathy or spontaneous bacterial peritonitis.

Patients with a MELD-Na score > 15 (model for end-stage liver disease sodium score) were also assigned to the individual component of liver transplantation. As this is a composite laboratory parameter, the MELD-Na score is not considered to be directly patient-relevant.

In addition, the other subcomponents represent patient-relevant endpoints.

During the study, one subject on elafibranor and no subject in the control arm experienced uncontrolled ascites requiring treatment. However, there was no statistically significant difference between the study arms.

No events occurred with the other subcomponents in both treatment arms.

*Itching*

The endpoint of itching is a patient-relevant endpoint in the therapeutic indication. The itching symptomatology was assessed as part of the study using the two instruments "PBC Worst Itch NRS" and "5-D Itch Scale" (5-D Itch).

The PBC Worst Itch Numeric Rating Scale (NRS) is a disease-specific instrument for measuring the intensity of itching. A subject assesses the intensity of their worst itching on an 11-point scale from "0" (= no itching) to "10" (= worst perceivable itching) within the last 24 hours in the evening or the last 7 days. In the ELATIVE study, the survey took place at every visit and continuously every evening using a digital patient diary.

The 5-D Itch consists of five domains: "Duration", "Severity", "Direction", "Disability" and "Distribution". The "Duration", "Severity" and "Direction" domains each consist of 1 item, while the "Disability" domain consists of 4 items. All items in these 4 domains are measured using a 5-point Likert scale. Each domain can achieve a value of 1 to 5 points, with the total number of points to be achieved between 5 and 25 points. Higher points indicate more severe pruritus. The reference period was 2 weeks.

Responder analyses with a response threshold of an improvement by at least 15% at week 52 of the ELATIVE study are available for both measurement instruments.

Based on the responder analyses, there was a statistically significant advantage of elafibranor over placebo for the 5-D Itch in the "Severity" and "Direction" domains. However, these advantages are neither reflected in the total score of the 5-D Itch nor in the "Duration", "Distribution" and "Disability" domains. Based on the responder analyses using the PBC Worst Itch NRS, there were no statistically significant differences between the treatment arms.

*Health status*

The health status of the patients is assessed as patient-relevant. It was assessed in the study using the visual analogue scale of the European Quality of Life 5-Dimensions 5-Levels questionnaire (EQ-5D-5L-VAS).

The participants use the EQ-5D-5L-VAS to rate their own general health status on the current day on a scale from "0" (= worst perceivable health status) to "100" (= best perceivable health status).

For this endpoint, results of the responder analyses are available for a response threshold of an improvement by at least 15% at week 52 of the ELATIVE study.

The responder analysis showed no statistically significant difference between the treatment arms for the EQ-5D-5L-VAS endpoint.

*Daytime sleepiness*

The endpoint of daytime sleepiness is considered patient-relevant in the present therapeutic indication, particularly against the background of nocturnal itching. In the study, daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS).

The ESS is a patient-reported questionnaire for measuring daytime sleepiness based on eight everyday situations. Depending on the everyday situation, a distinction is made between no (= 0 points), a low (= 1 point), a medium (= 2 points) and a high (= 3 points) probability of falling asleep. To analyse the questionnaire, the sum of the individual answers is calculated, i.e. the total score can be between 0 and 24.

For this endpoint, results of the responder analyses are available for a response threshold of an improvement by at least 15% at week 52 of the ELATIVE study.

The responder analysis showed no statistically significant difference between the treatment arms in the ESS endpoint.

*Fatigue*

The fatigue endpoint is a patient-relevant endpoint in this therapeutic indication and was assessed in the study using PROMIS Fatigue Short Form 7a.

It consists of 7 items: "General fatigue", "Severe fatigue", "Lack of energy", "Fatigue in the work environment", "Clear thinking", "Tiredness for bathing or showering" and "Energy for exertion". Each item can be rated with 1 to 5 points. For the first 6 questions, 1 point stands for "never", 2 points for "rarely", 3 points for "sometimes", 4 points for "often" and 5 points for "always". As the last question records the absence of fatigue, its range of values is inverse of the first 6 questions. This means that lower values always represent a low burden, while

higher values represent a higher burden. The total score can range from 7 to 35 points. Patients rate their symptoms over the previous 7 days.

For this endpoint, results of the responder analyses are available for a response threshold of an improvement by at least 15% at week 52 of the ELATIVE study.

The responder analysis showed no statistically significant difference between the treatment arms in the endpoint of PROMIS Fatigue Short Form 7a.

Quality of life

The PBC-40 questionnaire with the domains of general symptoms (7 items), itching (3 items), fatigue (11 items), cognitive functions (6 items), social domain and emotional domain was used to assess quality of life. It is considered a valid disease-specific instrument for measuring quality of life in patients with PBC.

For this endpoint, results of the responder analyses are available for a response threshold of an improvement by at least 15% at week 52 of the ELATIVE study.

The responder analysis showed a statistically significant advantage of elafibranor over placebo in the "Itching" domain of the PBC-40 questionnaire. In the other domains of the PBC-40 questionnaire ("General symptoms", "Fatigue", "Cognitive functioning", "Emotional functioning" and "Social functioning"), there were no statistically significant differences between the treatment arms.

Side effects

The safety results in the total population of the ELATIVE study showed no statistically significant differences between the treatment groups in terms of serious adverse events (SAEs) and severe adverse events (SAEs), or therapy discontinuation due to AEs. The overall rate of AEs is presented additionally.

Overall assessment

Results of the ELATIVE study, which compared elafibranor with placebo over a period of 52 weeks, are available for the benefit assessment of elafibranor for the treatment of adults with primary biliary cholangitis (PBC) and inadequate response or intolerance to ursodeoxycholic acid (UDCA).

Two deaths occurred in the elafibranor arm of the ELATIVE study. There was no statistically significant difference between the treatment arms.

In the morbidity endpoint category, the endpoints of clinical events, itching, health status, daytime sleepiness and fatigue were assessed. For the endpoint of itching, there were statistically significant advantages in the "severity" and "direction" domains of the 5-D Itch. However, these advantages were neither reflected in the total score of the 5-D Itch nor in the other domains. The PBC Worst Itch NRS also showed no statistically significant differences between the treatment arms for the endpoint of itching. Likewise, there were no statistically significant differences between the treatment arms for the other endpoints in the category of morbidity.

In the endpoint category of quality of life, there was a statistically significant advantage of elafibranor in the "Itching" domain of the PBC-40 questionnaire. In the other domains, there were no statistically significant differences between the treatment arms.

In the endpoint category of side effects, there were no statistically significant differences between the treatment arms.

In the overall assessment of the available results, a minor additional benefit of elafibranor is identified due to the shown advantage in the health-related quality of life.

Significance of the evidence

For the ELATIVE RCT presented, the risk of bias at study level is assessed as low.

However, there were uncertainties due to the consistency of the results of the Patient Reported Outcomes (PRO) for the itching symptom. The 5-D Itch and PBC Worst Itch NRS showed different results in the morbidity endpoint category. Within the evaluation of the 5-D Itch endpoint, some of the results between the responder analyses and the continuous MMRM analyses were inconsistent. In addition, there was a high risk of bias at endpoint level for the endpoint of PBC Worst Itch NRS.

Overall, the uncertainties mentioned with regard to the significance of the evidence result in a hint for an additional benefit.

### 2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of elafibranor finds its legal basis in Section 35a, paragraph 3, sentence 5 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

In view of the fact that further long-term data on the efficacy and safety of elafibranor based on the double-blind, randomised, placebo-controlled phase III ELFIDENCE study (NCT06016842) for patients with more advanced setting of the disease are expected, which may be relevant for the assessment of the benefit of the medicinal product, limiting the resolution (in time) until further scientific findings are available for the assessment of the additional benefit of elafibranor is justified. The limitation enables the expected results from the ELFIDENCE study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V.

For this purpose, the G-BA considers a limitation of the validity of the resolution until 1 December 2030 to be appropriate.

*Conditions of the limitation:*

For the new benefit assessment after expiry of the deadline, the results from the final analysis on efficacy and safety as well as on all other patient-relevant outcomes from the ELFIDENCE study expected in May 2030 must be presented in the dossier.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3 paragraph 1, number 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, number 7 VerfO, the procedure for the benefit assessment of the medicinal product with the active ingredient elafibranor recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of elafibranor (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may

determine that there is a non-quantifiable additional benefit because the required evidence is not complete.

The possibility that a benefit assessment for the medicinal product with the active ingredient elafibranor can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1 paragraph 2, Nos. 2 to 6 or No. 8 VerfO) remains unaffected hereof.

### 2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Iqirvo with the active ingredient elafibranor.

Iqirvo has been conditionally approved as an orphan drug for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA.

For the benefit assessment, the pharmaceutical company submitted the data from the label-enabling, multicentre, randomised, double-blind, placebo-controlled phase III ELATIVE study with a double-blind phase of 52 weeks.

No patients in a severely extensive-stage of primary biliary cholangitis were examined in the study. However, this patient group is covered by the marketing authorisation of elafibranor.

Two deaths occurred in the elafibranor arm of the study.

In the endpoint category of morbidity, there was no statistically significant difference between the treatment arms for the endpoints of clinical events, health status, daytime sleepiness and fatigue. Although there was a statistically significant advantage for the endpoint of itching in each of the "Severity" and "Direction" domains of the 5-D Itch, this was not reflected in the overall score of the 5-D Itch or in the other domains. The PBC Worst Itch NRS also showed no statistically significant differences between the treatment arms for the endpoint of itching.

In the endpoint category of health-related quality of life, there was a statistically significant advantage in the "Itching" domain of the PBC-40 questionnaire.

No statistically significant differences were observed between the treatment arms in the category of side effects.

In the overall assessment of the available results, a hint for a minor additional benefit of elafibranor is identified due to the shown advantage in the health-related quality of life.

The validity of the resolution is limited to 1 December 2030.

## 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 G24-30).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to uncertainties. These uncertainties arise due to the limited epidemiological data basis on the incidence and prevalence of a confirmed diagnosis of PBC, in particular for determining the upper and lower limits, as well as a lack of information on the percentage of patients treated with UDCA with an inadequate response or intolerance to UDCA.

## 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 Iqirvo (active ingredient: elafibranor) at the following publicly accessible link (last access: 25 March 2025):

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

This medicinal product received a conditional marketing authorisation. This means that further evidence of the benefit of the medicinal product is anticipated. The European Medicines Agency will evaluate new information on this medicinal product at a minimum once per year and update the product information where necessary.

## 2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 March 2025).

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.

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 | | | | |
| Elafibranor | 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 | | | | | |
| Elafibranor | 80 mg | 80 mg | 1 x 80 mg | 365 | 365 x 80 mg |

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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

**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 | | | | | |
| Elafibranor 80 mg | 30 FCT | € 5,900.71 | € 1.77 | € 333.70 | € 5,565.24 |
| Abbreviations: FCT = film-coated tablets | | | | | |

LAUER-TAXE® last revised: 15 March 2025

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 with primary biliary cholangitis (PBC) and inadequate response or intolerance to ursodeoxycholic acid (UDCA)

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 elafibranor (Iqirvo); Iqirvo 80 mg film-coated tablets; last revised: September 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 14 October 2024, the pharmaceutical company submitted a dossier for the benefit assessment of elafibranor 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 15 January 2025 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 5 February 2025.

The oral hearing was held on 24 February 2025.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 14 March 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 25 March 2025, and the proposed draft resolution was approved.

At their session on 3 April 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee on Medicinal Products | 7 January 2025 | Information of the benefit assessment of the G-BA |
| Working group Section 35a | 19 February 2025 | Information on written statements received; preparation of the oral hearing |
| Subcommittee on Medicinal Products | 24 February 2025 | Conduct of the oral hearing |
| Working group Section 35a | 5 March 2025<br>19 March 2025 | Consultation on the dossier evaluation by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure |
| Subcommittee on Medicinal Products | 25 March 2025 | Concluding discussion of the draft resolution |
| Plenum | 3 April 2025 | Adoption of the resolution on the amendment of the Pharmaceuticals Directive |

Berlin, 3 April 2025

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

Prof. Hecken