

Justification

to 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
Seladelpar (primary biliary cholangitis (combination with
ursodeoxycholic acid))**

of 4 September 2025

Contents

1.	Legal basis.....	2
2.	Key points of the resolution.....	3
2.1	Additional benefit of the medicinal product.....	4
2.1.1	Approved therapeutic indication of Seladelpar (Lyvdelzi) in accordance with the product information.....	4
2.1.2	Extent of the additional benefit and significance of the evidence.....	5
2.1.3	Time limit and period of validity of the resolution.....	8
2.1.4	Summary of the assessment	9
2.2	Number of patients or demarcation of patient groups eligible for treatment	9
2.3	Requirements for a quality-assured application	10
2.4	Treatment costs	10
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	12
2.6	Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V.....	15
3.	Bureaucratic costs calculation.....	15
4.	Process sequence	16

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess 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 decide 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 seladelpar on 15 March 2025 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 March 2025.

Seladelpar for the treatment of primary biliary cholangitis (combination with ursodeoxycholic acid) 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 16 June 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 made their 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 G25-13) and the statements made in the written statements and oral hearing process, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA have 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 seladelpar.

¹General 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 Seladelpar (Lyvdelzi) in accordance with the product information

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

Therapeutic indication of the resolution (resolution of 4 September 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 seladelpar is assessed as follows:

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

Justification:

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

The RESPONSE study is a multicentre, randomised, double-blind, placebo-controlled phase III study investigating the efficacy, safety and tolerability of seladelpar in patients with PBC with inadequate response or intolerance to UDCA. A total of 193 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. 128 subjects were randomised to the intervention arm and 65 subjects to the control arm in a 2:1 ratio.

A screening and run-in phase was followed by a treatment period of 12 months with the option of subsequently participating in the ASSURE open-label, long-term follow-up study. The primary endpoints of the study were the combined biochemical response at month 12 and adverse events. In addition, other endpoints in the categories of mortality, morbidity, health-related quality of life and side effects were assessed.

No patients in a severely extensive-stage of primary biliary cholangitis were examined in the RESPONSE study. In addition, only eight patients who showed intolerance to UDCA and received monotherapy with seladelpar were enrolled in the study. However, both patient groups are covered by the marketing authorisation of seladelpar.

The use of fibrates as part of the study was ruled out. Bezafibrate in particular is not approved for the treatment of PBC, but is recommended in the guidelines for the symptomatic treatment of itching. The significance of fibrates was also discussed during the written statement procedure.

Mortality

Deaths from any cause were collected as part of the safety assessment. There were no deaths in the study. Thus, there was no statistically significant difference between the study arms.

Morbidity

Biochemical response

The composite endpoint of biochemical response at month 12 versus baseline was the primary endpoint of the RESPONSE study. It comprises the response of the laboratory parameters alkaline phosphatase (ALP) and total bilirubin (TB) (ALP < 1.67 × ULN and ALP reduction ≥ 15% and TB ≤ 1.0 × ULN).

The endpoint of biochemical response showed a statistically significant advantage of seladelpar 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

Clinical PBC events were defined as the endpoints of liver transplantation, MELD score ≥ 15 (model for end-stage liver disease) on at least 2 consecutive visits, ascites requiring treatment, hospitalisation due to variceal haemorrhage, hepatic encephalopathy or spontaneous bacterial peritonitis and death.

These clinical events represent patient-relevant endpoints.

In the RESPONSE study, all clinical PBC events were assessed by both the investigators and a Clinical Event Review Committee (CERC).

There were hospitalisations in both the intervention and the control arms. However, there was no statistically significant difference between the study arms. No events occurred with the other endpoints in both treatment arms.

Itching

The endpoint of itching is a patient-relevant endpoint in the therapeutic indication. The assessment of the itching symptomatology in the RESPONSE study was carried out using the "PBC Worst Itch NRS" and "5-D Itch Scale" (5-D Itch) as well as the "Patient Global Impression of Change" (PGI-C) and "Patient Global Impression of Severity" (PGI-S).

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 RESPONSE study, the survey was conducted continuously every evening up to month 6, and on 7 consecutive days per month after month 6 using a digital patient diary.

The 5-D Itch Scale 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. In the RESPONSE study, the survey was conducted every 2 weeks up to month 6, and monthly after month 6 using a digital patient diary.

The PGI-S and PGI-C are not used for derivation of an additional benefit due to the double collection and the availability of more suitable measurement instruments for the itching symptomatology.

For the present assessment, the results of the evaluations of the continuous analyses at month 12 were generally used for the measurement instruments for the itching symptomatology. Only the results at month 6 are presented for this endpoint due to uncertainties in the survey caused by permissible deviations and the low return rates of the pruritus NRS in the period after month 6. Adequate responder analyses with an improvement by at least 15%, which would generally be preferable, were not presented for the ITT population.

There was a statistically significant advantage of seladelpar over placebo in the pruritus NRS as well as in the total score and all individual domains of the 5-D Itch Scale. Based on the respective Hedges' g , a clinically relevant effect can also be deduced from the statistically significant evaluation results of the Pruritus-NRS, the total score of the 5-D Itch and the "Impairment" domain of the 5-D Itch.

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.

In the RESPONSE study, the survey was conducted using an electronic diary with a reference period of 4 weeks and the evaluation of the change from baseline at the pre-specified times of the study visits was carried out.

In the present case, the results of the evaluations of the continuous analyses at month 12 were used for the benefit assessment. Adequate responder analyses with an improvement by at least 15%, which would generally be preferable, were not presented for the ITT population.

In the endpoint of PBC-40, there was no statistically significant difference between the treatment arms.

Side effects

The safety results in the total population of the RESPONSE study showed no statistically significant differences between the treatment groups in terms of serious adverse events (SAEs) and severe adverse events (CTCAE grade 3 or 4), or therapy discontinuation due to AEs. The overall rate of AEs is presented additionally.

In the AEs of special interest "Pruritus-related AEs (regardless of severity grade)", there was a statistically significant advantage of seladelpar over placebo, which, however, was not used further due to the other results on the itching symptomatology in the endpoint category of morbidity.

Overall assessment

Results of the RESPONSE study, which compared seladelpar with placebo over a period of 12 months, are available for the benefit assessment of seladelpar for the treatment of adults with primary biliary cholangitis (PBC) and inadequate response or intolerance to ursodeoxycholic acid (UDCA).

There were no deaths in the RESPONSE study.

In the endpoint category of morbidity, the patient-relevant endpoints of clinical events and itching were assessed. For the endpoint of itching, there was a statistically significant advantage of seladelpar over placebo in the Pruritus-NRS measurement instrument as well as in the total score and all individual domains of the 5-D Itch Scale respectively. There were no clinical events such as liver transplantations, a MELD score ≥ 15 or ascitis requiring treatment. In the endpoint of hospitalisation, there was no statistically significant difference between the treatment arms.

In the endpoint category of quality of life, there was no statistically significant difference between the treatment arms in the endpoint of PBC-40.

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

In the overall assessment of the available results, a minor additional benefit of seladelpar is identified due to the shown advantage in the endpoint of itching.

Significance of the evidence

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

At the endpoint level, there was a high risk of bias for the endpoint of 5-D Itch due to the unclear parallelism of the surveys and the handling of missing values between the study arms. In contrast, the endpoint of Pruritus-NRS at month 6 showed a low risk of bias.

The overall assessment results in an indication of an additional benefit due to the low risk of bias at study level and the consistent advantages in several endpoints for the itching symptomatology, despite the high risk of bias of the endpoint of 5-D Itch.

2.1.3 Time limit and period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of seladelpar 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 seladelpar based on the randomised, placebo-controlled clinical phase 3 AFFIRM study for adult patients with PBC and compensated liver cirrhosis 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 seladelpar is justified. The limitation enables the expected results from the AFFIRM 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 March 2031 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 endpoints from the AFFIRM study expected in August 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.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Lyvdelzi with the active ingredient seladelpar.

Lyvdelzi has been approved special conditions as an orphan drug for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA alone, or as monotherapy in those unable to tolerate UDCA.

For the benefit assessment, the pharmaceutical company submitted the data from the label-enabling, multi-centre, randomised, double-blind phase III RESPONSE study, which compared seladelpar with placebo over a period of 12 months.

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 seladelpar.

There were no deaths in the study.

In the endpoint category of morbidity, the patient-relevant endpoints of clinical events and itching were assessed. For the endpoint of itching, there was a statistically significant advantage of seladelpar over placebo in the Pruritus-NRS measurement instrument as well as in the total score and all individual domains of the 5-D Itch Scale respectively. There were no clinical events such as liver transplantations, a MELD score ≥ 15 or ascitis requiring treatment. In the endpoint of hospitalisation, there was no statistically significant difference between the treatment arms.

In the endpoint category of quality of life, there was no statistically significant difference between the treatment arms in the endpoint of PBC-40.

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

In the overall assessment of the available results, an indication of a minor additional benefit of seladelpar is identified due to the shown advantage in the endpoint of itching.

The validity of the resolution is limited to 1 March 2031.

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).

Due to the recommendation from IQWiG's dossier assessment (mandate G25-13), the resolution is based on the information in the resolution on the active ingredient elafibanor from 3 April 2025².

² <https://www.g-ba.de/beschluesse/7144/>

Overall, the patient numbers presented in the pharmaceutical company's dossier are comparable to the patient numbers for the benefit assessment of elafibranor, despite the different approach. Even though both derivations are subject to uncertainty, the data on elafibranor are used because the range of the percentage of patients who respond inadequately to treatment with UDCA is considered more appropriate.

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 Lyvdelzi (active ingredient: seladelpar) at the following publicly accessible link (last access: 26 August 2025):

https://www.ema.europa.eu/en/documents/product-information/lyvdelzi-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 contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 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 comorbidities) 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.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2021 – body measurements of the population" were used as a basis (average body weight: 77.7 kg)³.

³ Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

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				
Seladelpar	Continuously, 1 x daily	365	1	365
Ursodeoxycholic acid	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					
Seladelpar	10 mg	10 mg	1 x 10 mg	365	365 x 10 mg
Ursodeoxycholic acid	1000 mg	1000 mg	4 x 250 mg	365	1460 x 250 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					
Lyvdelzi 10 mg hard capsule	90 HC	€ 16,681.71	€ 1.77	€ 949.40	€ 15,730.54
UDC AL 250 mg hard capsules ⁴	100 HC	€ 39.66	€ 1.77	€ 2.24	€ 35.65
Abbreviations: HC = hard capsules					

⁴ Fixed reimbursement rate

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 designate 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 have 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 have 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 have 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 that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for seladelpar (Lyvdelzi); Lyvdelzi® (formerly Gilead's seladelpar) 10 mg hard capsules; last revised: May 2025

2.6 Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Lyvdelzi is a medicinal product placed on the market from 1 January 2025. In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV. Approval studies include all studies submitted to the regulatory authority in the authorisation dossier for the assessment of the clinical efficacy and safety of the medicinal product in the therapeutic indication to be assessed.

The pharmaceutical company provides information on the four studies (CB8025-32048, CB8025-31735, CB8025-21528, CB8025-21629) and states the percentage of study participants at study sites within the scope of SGB V as 4.84% for the present therapeutic indication and the associated patient population across all relevant studies.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is < 5% of the total number of study participants.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant extent within the scope of SGB V.

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 March 2025, the pharmaceutical company submitted a dossier for the benefit assessment of seladelpar 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 16 June 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 7 July 2025.

The oral hearing was held on 28 July 2025.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 15 August 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 26 August 2025, and the draft resolution was approved.

At their session on 4 September 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	11 June 2025	Information of the benefit assessment of the G-BA
Working group Section 35a	15 July 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	28 July 2025	Conduct of the oral hearing
Working group Section 35a	5 August 2025 19 August 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 on Medicinal Products	26 August 2025	Concluding discussion of the draft resolution
Plenum	4 September 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 4 September 2025

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

Prof. Hecken