Gemeinsamer Bundesausschuss

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
Resmetirom (noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH))

From 5 March 2026

Contents

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. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical studies the pharmaceutical company have conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application,
7. number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment 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 resmetirom on 15 September 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO). Pursuant to Section 4, paragraph 3, No. 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, No. 1 Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 12 September 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 December 2025 on the G-BA website at (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of resmetirom compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements

submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA have evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of resmetirom.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have made the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Resmetirom (Rezdiffra) in accordance with the product information

Resmetirom is indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3).

Therapeutic indication of the resolution (resolution of 05.03.2026):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3)

Appropriate comparator therapy for resmetirom in conjunction with diet and exercise:

- Optimised standard therapy for the treatment of comorbidities such as diabetes mellitus, hypertension, obesity and lipid metabolism disorders

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5 Section 6, paragraph 3 VerfO:

[1] General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if they determine by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

On 1. No medicinal products other than the active ingredient resmetirom to be assessed are approved in the present therapeutic indication.

On 2. Non-medicinal treatments are not considered in the direct therapeutic indication.

On 3. In the present therapeutic indication, there are currently no resolutions of the G-BA regarding an amendment to Annex XII of the Pharmaceuticals Directive (AM-RL) on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present indication according to Section 35a paragraph 7 SGB V (see "Information on Appropriate Comparator Therapy").

In the present therapeutic indication, a European guideline (European Association for the Study of the Liver et al., 2024), an Italian guideline (AISF, SID, SIO, 2021) and an American guideline (Cusi K et al., 2022) on the management of metabolic dysfunction-associated steatotic liver disease (MASLD) were identified. The guidelines recommend standard therapy for the treatment of comorbidities such as diabetes mellitus or cardiovascular disease, as well as weight reduction measures (e.g. dietary changes, physical exercise, and, where indicated, bariatric surgery), although no specific recommendation can be derived for any specific type of diet.

Furthermore, the available evidence on pharmacological treatment options only allow identification of experimental approaches (e.g. vitamin E, omega-3 fatty acids or cholic acid derivatives) which, due to a lack of marketing authorisation in the therapeutic indication, cannot be considered as appropriate comparator therapy.

Against this background, the G-BA determined the appropriate comparator therapy to be an optimised standard therapy for the treatment of comorbidities such as diabetes mellitus, hypertension, obesity and lipid metabolism disorders.

It is assumed that patient-individual treatment of comorbidities such as diabetes mellitus, hypertension, obesity and lipid metabolism disorders is carried out according to the state of medical knowledge, taking into account the specific characteristics of the actual disease and the German healthcare context. Standard therapy should also include non-medicinal measures such as recommendations for weight reduction and exercise, where indicated. In individual cases, surgical intervention (e.g. bariatric surgery) may be indicated for severely obese subjects. This does not represent a standard therapy option in the present therapeutic indication and is therefore not part of the determined appropriate comparator therapy.

The relevant findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

Any change to the appropriate comparator therapy requires a decision by the G-BA based on a prior review of the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO.

2.1.3 Extent and probability of the additional benefit

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

Adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3)

An additional benefit is not proven.

Justification:

The pharmaceutical company presented results of the ongoing, multicentre, double-blind, placebo-controlled, phase III MAESTRO-NASH study for the benefit assessment of resmetirom for the treatment of adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3). In

addition, the pharmaceutical company presented the results of a sub-population of the double-blind, placebo-controlled MAESTRO-NAFLD-1 study and the completed double-blind RCT MGL-3196-05.

With regard to the MAESTRO-NAFLD-1 study, there are uncertainties as to whether the indication for resmetirom therapy was given, based on the degree of fibrosis in the patients included in the sub-population, whether the implementation of the appropriate comparator therapy was sufficiently guaranteed, and due to the missing adjustments to the evaluation in terms of body weight. The MGL-3196-05 study was only supportively presented in the dossier by the pharmaceutical company due to the significantly reduced sub-population as a result of the cut-off as well as the unequal study arms.

Therefore, the two supportive studies are not used for derivation of an additional benefit, and the results of the MAESTRO-NASH study are presented below.

A total of 1,050 patients were enrolled in the MAESTRO-NASH study, randomised in a 1:1:1 ratio (resmetirom 80 mg (N = 352), resmetirom 100 mg (N = 349), placebo (N = 349)) and stratified by the presence of type 2 diabetes mellitus and the stage of fibrosis. There had to be a diagnosis of MASH with liver fibrosis (fibrosis stages F1 to F3) confirmed by a recent liver biopsy and a non-alcoholic fatty liver disease activity score (NAS) of at least 4, with at least 1 point in each of the NAS components (steatosis, ballooning and lobular inflammation).

At the start of the study, all patients received lifestyle counselling with recommendations on diet and exercise. In addition, stabilised medicinal treatments for existing comorbidities could be continued in the study. Overall, based on the information presented with the dossier, it was not possible to assess whether adequate treatment of type 2 diabetes mellitus was ensured despite the limitation of antidiabetic therapy optimisation in the study. Furthermore, it remained unclear whether the applicable limitations of lipid-lowering therapy in the study allowed for adequate implementation of appropriate therapy for dyslipidaemia.

In response to criticism in the benefit assessment on the adequate implementation of the appropriate comparator therapy, the pharmaceutical company subsequently submitted data on the medicinal treatment of type 2 diabetes mellitus and the medicinal treatment of dyslipidaemia. Overall, there is no indication that the antidiabetic therapy in the study was inadequate for a relevant percentage of patients during the period under review. However, the subsequently submitted data on dyslipidaemia cannot completely dispel the uncertainty as to whether patients in the placebo arm received optimum treatment despite the limited dosage options for statins. However, no relevant impact on the results is expected for the present evaluation time points.

The planned comparative treatment duration of the MAESTRO-NASH study is up to 54 months. Results from the pre-specified analysis time point at week 52 are available for the benefit assessment, and results for a period of up to 3.5 years are available for the side effects.

The primary endpoints of this analysis at week 52 are NASH resolution response and fibrosis response. The primary endpoint of the analysis at month 54 is a composite endpoint comprising all-cause mortality, liver transplantation, and other major liver-related events. In addition, endpoints in the categories of morbidity, health-related quality of life and side effects are collected at both analysis time points.

As part of the written statement procedure, the pharmaceutical company also submitted analyses with a weight-adjusted analysis population, responder analyses of improvement and deterioration, and information on concomitant medication used in the study, which were also taken into account in the benefit assessment.

Extent and probability of the additional benefit

Mortality

Deaths were recorded in the MAESTRO-NASH study as part of the safety assessment. There were two deaths in the resmetirom arm and one death in the placebo arm. There was no statistically significant difference between the treatment groups.

Morbidity

Major adverse cardiac events (MACE)

In the MAESTRO-NASH study, MACE is defined as a composite endpoint comprising three individual components: cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke. Assessment was made as part of the side effects.

The individual components generally represent patient-relevant endpoints.

The results cannot be presented due to the absence of information on the operationalisation of the individual components in the dossier or the study protocol.

In the composite endpoint MACE, there was no statistically significant difference between the treatment groups.

Fibrosis response

Fibrosis response was one of the primary endpoints of the interim analysis of the MAESTRO-NASH study at week 52. Histological improvement based on liver biopsies at week 52 (± 10 days) compared to baseline was considered. The liver biopsies were evaluated centrally by two blinded pathologists. The fibrosis stage was determined based on the NASH Clinical Research Network scale and is operationalised as an improvement by ≥ 1 fibrosis stage without deterioration of NAS compared to baseline.

Endpoints based on imaging or histological assessments, such as fibrosis response, are not per se patient-relevant. Furthermore, there is insufficient evidence overall to prove that this endpoint is a sufficiently valid surrogate for patient-relevant endpoints such as mortality, avoidance or delay of liver transplantation, or symptomatic progression to cirrhosis of the liver.

However, this endpoint is presented additionally as the change in fibrosis stage is an important prognostic factor.

Quality of life

Short Form-36 Health Survey Version 2 (SF-36v2)

SF-36 comprising eight domains and a total of 36 questions is a generic tool for measuring health-related quality of life. In addition, the 8 domains are summarised into a physical component summary (PCS) score and a mental component summary (MCS) score. For the domain and summary scores, higher values mean a better health-related quality of life.

As part of the written statement procedure, the pharmaceutical company submitted responder analyses of the percentage of patients with an improvement or deterioration by at least 15% of the scale range at week 52. For the SF-36, no data is available on the normative sample on which these evaluations are based. Due to the expected course of the disease in the present therapeutic indication and taking into account the distribution of the absolute values of the scales at the start of the study, the evaluation of the deterioration in health-related quality of life is used.

For health-related quality of life, assessed using SF-36v2, there was no statistically significant difference between the treatment groups for either the physical component summary (PCS) score or the mental component summary (MCS) score.

Chronic Liver Disease Questionnaire (CLDQ) NAFLD/NASH

The CLDQ-NAFLD/NASH is a tool for assessing health-related quality of life in patients with metabolic dysfunction-associated steatotic liver disease (MASLD) or MASH.

The version of the tool used in the MAESTRO-NASH study consists of 36 items with 6 scales (abdominal symptoms, activity/ energy, emotional health, fatigue, systemic symptoms and worries). Each item is answered on a Likert scale of 1 to 7 points. The total score used has a scale range of 6 points.

As part of the written statement procedure, the pharmaceutical company submitted responder analyses of the percentage of patients with an improvement or deterioration by at least 15% of the scale range at week 52. Due to the expected course of the disease in the present therapeutic indication and taking into account the distribution of the absolute values of the scales at the start of the study, the evaluation of the deterioration in health-related quality of life is used.

For the health-related quality of life, assessed using CLDQ-NAFLD/NASH, there was no statistically significant difference between the treatment groups.

Side effects

For the overall rates of side effects collected, evaluations excluding disease-related events are used in each case. The pharmaceutical company defines the events of hepatic cirrhosis, ascites, oesophageal varices, haemorrhage and hepatic encephalitis as disease-related.

For the overall rates of serious adverse events (SAEs), severe AEs (CTCAE grade ≥ 3) and discontinuation due to AEs, there were no statistically significant differences between the treatment groups.

Detailed analysis of the endpoints of gastrointestinal disorders and vascular disorders shows a statistically significant difference to the advantage of resmetirom compared to placebo. These are endpoints based on severe and serious adverse events at the system organ class (SOC) level.

Furthermore, detailed analysis of the endpoint of diarrhoea shows a statistically significant difference to the disadvantage of resmetirom compared to placebo. For this endpoint, there was an effect modification due to the sex characteristic. For men, there was a statistically significant disadvantage of resmetirom compared to placebo, while for women, there was no statistically significant difference between the treatment groups. These are endpoints based on non-severe and non-serious adverse events at the PT level.

Overall assessment

Results from the interim analysis of the ongoing MAESTRO-NASH study at week 52 are available for the benefit assessment of resmetirom in conjunction with diet and exercise for the treatment of adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3). This is a multicentre, double-blind, controlled, phase III study of resmetirom versus placebo, each with treatment of the existing comorbidities with a planned study duration of 54 months.

With regard to mortality, there were no statistically significant differences between the treatment groups.

For the endpoint of major adverse cardiac events (MACE) in the endpoint category of morbidity, there was no statistically significant difference between the treatment groups.

For the health-related quality of life, the evaluations based on the SF-36v2 and the CLDQ-NAFLD/NASH did not show any statistically significant difference between the treatment groups.

For the overall rates of serious adverse events, severe adverse events and therapy discontinuation due to adverse events in the endpoint category of side effects, there was no statistically significant difference between the treatment groups. Detailed analysis of the endpoints of gastrointestinal disorders and vascular disorders shows a statistically significant advantage of resmetirom, while that of the endpoint of diarrhoea shows a statistically significant disadvantage of resmetirom. Overall, no relevant differences for the benefit assessment were derived in the category of side effects.

In the overall assessment, based on the interim analysis of the MAESTRO-MASH study, no relevant differences for the benefit assessment were identified in the endpoint categories of mortality, morbidity, health-related quality of life and side effects. An additional benefit of resmetirom in conjunction with diet and exercise for the treatment of adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3) is therefore not proven.

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of resmetirom 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.

The data from the MAESTRO-NASH study (MGL-3196-11; NCT03900429) at the analysis time point at week 52 are used for the present assessment. Among others, data are available on the primary endpoints of NASH resolution response and fibrosis response at week 52, as well as other endpoint categories.

On the contrary, the final results from the still ongoing study, particularly with regard to the primary composite endpoint at month 54, are still pending. Further results at month 54 are expected for a composite endpoint comprising components such as all-cause mortality, liver transplantation and liver-related events. In addition, further data on the endpoint categories of morbidity, health-related quality of life and side effects will also be collected at month 54.

Since clinical data on overall survival and on additional patient-relevant endpoints of the morbidity, quality of life and side effects category which may be relevant for the benefit assessment of the medicinal product are expected, it is justified to limit the validity of the resolution in order to take further scientific findings into account for the assessment of the additional benefit of resmetirom. The limitation enables the expected final results from the MAESTRO-NASH (MGL-3196-11; NCT03900429) study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V.

For this purpose, limitation of the validity of the resolution until 1 October 2029 is considered appropriate.

<u>Conditions of the limitation:</u>
For the new benefit assessment after the expiry of the deadline, the results of the final data cut-off from the MAESTRO-NASH (MGL-3196-11; NCT03900429) study 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 period is insufficient or too long.

In accordance with Section 3, paragraph 1, No. 5 AM-NutzenV in conjunction with Chapter 5 Section 1, paragraph 2, No. 7 VerfO, the benefit assessment procedure of the medicinal product with the active ingredient resmetirom recommences when the deadline has expired. For this purpose, the pharmaceutical company must present a dossier to the G-BA at the latest on the date of expiry of the deadline for proof of an additional benefit of resmetirom in comparison with the appropriate comparator therapy (Section 4, paragraph 3, No. 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, No. 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit is considered not proven.

This does not affect the possibility that a benefit assessment of the medicinal product with the active ingredient resmetirom may be carried out at an earlier date for other reasons (see Chapter 5 Section 1, paragraph 2, Nos. 2 to 6 or 8 VerfO).

2.1.5 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Rezdiffra with the active ingredient resmetirom.

The active ingredient is indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3).

The G-BA determined the appropriate comparator therapy to be an optimised standard therapy for the treatment of comorbidities such as diabetes mellitus, hypertension, obesity and lipid metabolism disorders.

For the benefit assessment of resmetirom, the pharmaceutical company submitted the results of the interim analysis of the ongoing MAESTRO-NASH study at week 52. This is a multicentre, double-blind, controlled, phase III study on resmetorim versus placebo, each with treatment of the existing comorbidities with a planned study duration of 54 months.

In the endpoint categories of mortality, morbidity due to the endpoint of major adverse cardiac events (MACE) and health-related quality of life based on the SF-36v2 and CLDQ-NAFLD/NASH, there was no statistically significant difference between the treatment groups.

For the overall rates of serious adverse events, severe adverse events and therapy discontinuation due to adverse events in the endpoint category of side effects, there was no statistically significant difference between the treatment groups. Detailed analysis of the endpoints of gastrointestinal disorders and vascular disorders shows a statistically significant advantage of resmetirom, while that of the endpoint of diarrhoea shows a statistically significant disadvantage of resmetirom. Overall, no relevant differences for the benefit assessment were derived in the category of side effects.

In the overall assessment, an additional benefit of resmetirom compared to the appropriate comparator therapy is not proven.

The resolution is limited to 1 October 2029.

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 G-BA take into account the patient numbers stated in the pharmaceutical company's dossier. However, these are subject to uncertainty due to the limited epidemiological data basis on the incidence and prevalence of the MASH indication, the diagnoses used based on ICD-10-GM and Operations and Procedure Codes (OPC), the different approaches to diagnosis in the literature reviewed, and the lack of extrapolation to the year 2025. Overall, an underestimation of the patient numbers can be assumed.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Rezdiffra (active ingredient: resmetirom) at the following publicly accessible link (last access: 24 February 2026):

https://www.ema.europa.eu/en/documents/product-information/rezdiffra-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 (EMA) will assess new information on this medicinal product at least annually 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: 1 January 2026). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different 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 recommended dosage according to the product information is based on body weight. 80 mg is recommended for patients with a body weight < 100 kg, while 100 mg once daily is recommended for patients with a body weight ≥ 100 kg.

Adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3)

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				
Resmetirom	Continuously, 1 x daily	365.0	1	365.0
Optimised standard therapy		Different from patient to patient		
Appropriate comparator therapy				
Optimised standard therapy for the treatment of comorbidities such as diabetes mellitus, hypertension, obesity and lipid metabolism disorders				
Optimised standard therapy		Different from patient to patient		

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					
Resmetirom	BW < 100 kg 80 mg	80 mg	1 x 80 mg	365.0	365.0 x 80 mg
	BW ≥ 100 kg 100 mg	100 mg	1 x 100 mg	365.0	365.0 x 100 mg
Appropriate comparator therapy					
Optimised standard therapy for the treatment of comorbidities such as diabetes mellitus, hypertension, obesity and lipid metabolism disorders					
Optimised standard therapy		Different from patient to patient			

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					
Resmetirom 80 mg	28 FCT	€ 2,618.58	€ 1.77	€ 146.26	€ 2,470.55
Resmetirom 100 mg	28 FCT	€ 2,618.58	€ 1.77	€ 146.26	€ 2,470.55
Abbreviations: FCT = film-coated tablets					

LAUER-TAXE® last revised: 15 December 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.

Because there are no 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, no costs for additionally required SHI services had to be taken into account.

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 data from the product information on active ingredients within the scope of this therapeutic indication.

<u>Concomitant active ingredient</u>

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 statutory 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 noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (fibrosis stages F2 to F3)

No medicinal product with new active ingredients for use in combination therapy in compliance with the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for resmetirom (Rezdiffra); Rezdiffra 60/80/100 mg film-coated tablets; last revised: 18 August 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 Rezdiffra 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 section 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety) of the authorisation dossier in the therapeutic indication for which marketing authorisation has been applied for. In addition, studies, which were conducted in whole or in part within the therapeutic

indication described in this document, and in which the company was a sponsor or is otherwise financially involved, must also be indicated.

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% (1.29%) of the total number of study participants according to the information provided by the pharmaceutical company.

The pharmaceutical company provides information on a total of six studies. However, the MAESTRO-NASH-OUTCOMES study was not submitted as part of the authorisation dossier for the assessment of safety and efficacy. In addition, nine further studies with study registry entries, all of which were conducted in the USA, were identified in comparison with the Common Technical Document.

For the MAESTRO-NASH study, there was a discrepancy between the information provided by the pharmaceutical company in Module 3 A and/or the information provided in the SAS extracts (data cut-off from 31 July 2022) made available by the pharmaceutical company on the one hand and the information in the study registry (last revised 11 October 2023) on the other with regard to the number of patients enrolled.

Subject to the discrepancy described above and taking into account the additional studies identified and the information provided by the pharmaceutical company on the relevant studies, the percentage of study participants at study sites within the scope of SGB V remains below 5%.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore not conducted to a relevant percentage 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

At their session on 23 April 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 12 September 2025, the pharmaceutical company submitted a dossier for the benefit assessment of resmetirom to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 16 September 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient resmetirom.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 December 2025, and the written statement procedure was initiated with publication on the G-BA website on 15 December 2025. The deadline for submitting statements was 5 January 2026.

The oral hearing was held on 27 January 2026.

By letter dated 27 January 2026, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 13 February 2026.

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 subcommittee session on 24 February 2026, and the draft resolution was approved.

At their session on 5 March 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	23 April 2025	Determination of the appropriate comparator therapy
Working group Section 35a	20 January 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	26 January 2026	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	3 February 2026 17 February 2026	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	24 February 2026	Concluding discussion of the draft resolution
Plenum	5 March 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 5 March 2026

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken