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
Bulevirtide (reassessment of an orphan drug after exceeding the EUR 30 million turnover limit (hepatitis delta virus (HDV) infection, HDV-RNA positive, ≥ 3 years, ≥ 10 kg BW))

of 19 February 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. requirement for a quality-assured application,

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 active ingredient bulevirtide (Hepcludex) was listed for the first time on 1 September 2020 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices. Hepcludex for the treatment of hepatitis delta virus (HDV) infection, HDV-RNA positive, ≥ 3 years, ≥ 10 kg body weight is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

At their session on 18 February 2021, the G-BA decided on the benefit assessment of bulevirtide in the therapeutic indication "for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adults with compensated liver disease" in accordance with Section 35a SGB V. The validity of the resolution adopted by the G-BA on 18 February 2021 has been limited to 1 June 2025.

Pursuant to Section 4, paragraph 3, No. 5 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, No. 5

Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 30 May 2025.

On 26 November 2024, bulevirtide received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 19 December 2024, i.e. at the latest within four weeks of informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient bulevirtide with the new therapeutic indication for the treatment of chronic hepatitis delta virus (HDV) infection in paediatric patients.

If the sales of the orphan drug through the statutory health insurance at pharmacy sales prices and outside the scope of SHI-accredited medical care, including value-added tax, exceed an amount of € 30 million in the last twelve calendar months, the pharmaceutical company must submit evidence in accordance with Chapter 5 Section 5, paragraphs 1 to 6 Rules of Procedure (VerfO) within three months of being requested to do so by the Federal Joint Committee, and in this evidence, must demonstrate the additional benefit compared to the appropriate comparator therapy.

The medicinal product Hepcludex exceeded the turnover limit of EUR 30 million by 28 February 2025 at the latest. By adoption of the resolution on 18 June 2025, following the finding that sales of the proprietary medicinal product Hepcludex with the active ingredient bulevirtide exceeded the turnover limit of EUR 30 million according to Section 35a, paragraph 1, sentence 12 SGB V, the G-BA therefore discontinued both the benefit reassessment procedure after the expiry of the deadline and the benefit assessment procedure in the new therapeutic indication according to Section 35a, paragraph 1, sentence 11 SGB V in conjunction with Chapter 5 Section 12 No. 1 Rules of Procedure of the G-BA.

By letter dated 27 June 2025, the pharmaceutical company was requested to submit a dossier for the benefit assessment according to Section 35a SGB V by 1 September 2025, due to exceeding the EUR 30 million turnover limit within the period from March 2024 until the end of February 2025. Pursuant to Section 4, paragraph 3, No. 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, No. 6 Rules of Procedure, the pharmaceutical company submitted the final dossier to the G-BA in due time on 1 September 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 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 bulevirtide compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG and the statements submitted in the written statement and oral hearing procedure. 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 bulevirtide.

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 bulevirtide (Hepcludex) in accordance with the product information

Hepcludex is indicated for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult and paediatric patients 3 years of age and older weighing at least 10 kg with compensated liver disease.

Therapeutic indication of the resolution (resolution of 19.02.2026):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with chronic hepatitis D infection with compensated liver disease

Appropriate comparator therapy for bulevirtide:

Best supportive care

b) Children and adolescents 3 to < 18 years of age with chronic hepatitis D infection and compensated liver disease

Appropriate comparator therapy for bulevirtide:

Best supportive care

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 in accordance with 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.

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

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. 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. In the present therapeutic indication, no other medicinal product apart from the active ingredient bulevirtide is approved for the treatment of chronic HDV infection in paediatric and adult patients.

On 2. A non-medicinal treatment cannot be considered in the present therapeutic indication.

On 3. In the therapeutic indication, there is a resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V on the active ingredient bulevirtide dated 18 February 2021 for the treatment of chronic HDV infection in adults.

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”).

The evidence in the present therapeutic indication is limited. Currently, bulevirtide is the only active ingredient approved for the treatment of chronic HDV infection. Since HDV infection always involves co-infection with hepatitis B (HBV infection), the S3 guideline of the German Society for Gastroenterology, Digestive and Metabolic Diseases recommends adequate treatment of HBV infection for the treatment of HBV/HDV infection. The guideline is aimed at children and adolescents as well as adults with HBV infection and HDV co-infection. The use of pegylated interferon (peginterferon) alfa will be reviewed in all patients with chronic HBV/HDV co-infection and compensated liver disease. The addendum "Antiviral therapy for chronic hepatitis D virus infection" to the S3 guideline was created with regard to the availability of bulevirtide and lists bulevirtide and peginterferon alfa as therapy options with antiviral efficacy against HDV infection. According to the addendum, the advantages and disadvantages of the two therapeutic concepts should be weighed up against each other and discussed with patients. Peginterferon alfa is not approved for the treatment of HDV infection.

During the written statement procedure, attention was also drawn to the high side effects profile of interferons, and it was emphasised that peginterferon alfa plays only a minor role in healthcare due to its contraindications.

Particularly in light of the fact that no other active ingredients are approved, the G-BA determined that best supportive care is the appropriate comparator therapy for bulevirtide in the treatment of children, adolescents and adults with chronic HDV infection. "Best supportive care" is defined as the therapy that provides the best possible, patient-individually optimised, supportive treatment to alleviate symptoms and improve quality of life.

As part of the appropriate comparator therapy, adequate treatment of the underlying HBV infection according to the generally recognised state of medical knowledge is required; according to the S3 guideline, the use of peginterferon alfa for the treatment of HBV infection should be reviewed in patients with chronic HBV/HDV co-infection.

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 bulevirtide is assessed as follows:

The additional benefit is not proven for adults with chronic hepatitis D infection with compensated liver disease.

The additional benefit is not proven for children and adolescents 3 to < 18 years of age with chronic hepatitis D infection and compensated liver disease.

Justification:

a) Adults with chronic hepatitis D infection and compensated liver disease

The pharmaceutical company presented the results of the MYR301 study for adult patients. As part of the marketing authorisation, the EMA requested further clinical data on the safety and efficacy of bulevirtide for review. With the completion of the MYR301 study, this requirement was deemed to have been met as part of a reassessment by the EMA, resulting in the conversion of bulevirtide's marketing authorisation from conditional to regular marketing authorisation.

The resolution on the benefit assessment of bulevirtide dated 18 February 2021 was limited in time in order to allow the additional data to be submitted by the pharmaceutical company during the marketing authorisation procedure to be taken into account in the assessment of the additional benefit. The submission of data from the MYR301 study thus fulfils the requirements of the time limit applied to the resolution of 18 February 2021.

The MYR301 study is a multicentre, randomised, open-label phase III study for the assessment of the safety and efficacy of bulevirtide. It was conducted between April 2019 and August 2024 at 16 study sites in Germany, Italy, Russia and Sweden. Adults 18 to 65 years of age with chronic HBV and HDV infection who tested positive for HDV-RNA in serum/ plasma at the time of screening and had elevated alanine aminotransferase levels were enrolled. It was randomised in a 1:1:1 ratio to three study arms with treatment of 2 mg/day bulevirtide, 10 mg/day bulevirtide and no treatment over a period of 48 weeks, followed by 10 mg/day bulevirtide. The total treatment duration with bulevirtide was 144 weeks in each study arm, followed by a 96-week follow-up period. The study arm with 10 mg/d bulevirtide does not correspond to the marketing authorisation and is therefore not considered in the benefit assessment.

In the comparator arm, in which no hepatitis D-specific treatment was administered during the first 48 weeks, study participants were allowed to receive nucleoside/ nucleotide analogues for the treatment of HBV infection, which was the case in 63% of participants. The treatment is considered to be an adequate implementation of the appropriate comparator therapy of best supportive care. Uncertainties however remain, as it is unclear to what extent the use of peginterferon alfa for the treatment of HBV infection would have been an alternative for patients in the comparator arm after appropriate testing in accordance with the guideline recommendations. Taking into account patient characteristics, it is assumed that a relevant percentage of patients treated with nucleoside/ nucleotide analogues in the MYR301 study could also have received treatment for chronic HBV infection with peginterferon alfa in accordance with the marketing authorisation and guidelines, and that this would potentially have been carried out in the German healthcare context.

In the comparator arm of the study, study participants are adjusted to 10 mg/d bulevirtide after 48 weeks, meaning that no data is available from this point onwards for comparison with the appropriate comparator therapy.

The first 48 weeks of the study, which allow a comparison between 2 mg/day bulevirtide (N = 49) and best supportive care (N = 51), are therefore relevant for the benefit assessment. The demographic and clinical characteristics of the study participants were largely balanced between the two treatment arms. The primary endpoint was the combined (virological and biochemical) response at week 48. In addition, endpoints on morbidity, health-related quality of life and side effects were also assessed.

Mortality

No deaths occurred in the MYR301 study during the relevant observation period (48 weeks).

Morbidity

Liver-related events

The composite endpoint of liver-related events, defined as the development of cirrhosis, development or deterioration of jaundice, coagulation disorders, ascites, hepatic encephalopathy, bleeding from oesophageal varices, development of hepatocellular carcinoma, liver transplantation, liver-related hospitalisations or liver-related death, was assessed. No events occurred in either study arm during the relevant observation period of 48 weeks. Even though the composite endpoint includes events, whose direct patient relevance is uncertain, it can be used for the benefit assessment, as no events occurred in either study arm during the relevant observation period of 48 weeks.

Fatigue

Fatigue was assessed as a patient-reported endpoint using the "Fatigue Severity Scale" (FSS) questionnaire. The FSS is a generic questionnaire for assessing the severity of fatigue symptoms and their impact on patients' daily routine. The FSS consists of 9 items that are rated on a 7-point scale (1 = complete rejection of the statement; 7 = complete agreement). Higher values indicate a greater degree of fatigue. The responder analysis of improvement by at least 15% of the scale range at week 48 is used for the benefit assessment. There was no statistically significant difference between the treatment arms.

Health status

The endpoint of health status was assessed using the visual analogue scale of EQ-5D. The response to the improvement in week 48 was also operationalised here as an improvement by at least 15% of the scale range. An increase in score by ≥ 15% of the scale range compared to the start of the study is considered as clinically relevant improvement. There was no statistically significant difference between the treatment arms.

Virological response

The primary endpoint of the study was the combined virological and biochemical response. The composite endpoint was defined as the simultaneous occurrence of virological response (undetectable HDV-RNA [LOD = 6 IU/ml] or a decrease in HDV-RNA by ≥ 2 $\log_{10}$ IU/ml compared to the start of the study) and biochemical response (normalisation of alanine aminotransferase (ALT)).

There is currently inadequate data available for validation as a surrogate parameter for the prevention of liver-related patient-relevant morbidity endpoints (e.g. development of liver fibrosis/ cirrhosis, development of hepatocellular carcinoma) or the endpoint of mortality.

However, the virological response is a significant endpoint for assessment of the clinical course of HDV infection and is therefore presented additionally.

For the virological response, there was a statistically significant advantage in favour of bulevirtide over best supportive care, based on the component "reduction in viral load by ≥ 2

log_{10}". In contrast, there was no statistically significant difference between the treatment arms in the component "undetectable HDV-RNA".

Health-related quality of life

Hepatitis Quality of Life Questionnaire (HQLQ/SF-36)

Health-related quality of life was assessed using the Hepatitis Quality of Life Questionnaire (HQLQ), which surveys generic and disease-specific well-being. It consists of the generic SF-36 tool and four additional hepatitis-specific domains (a total of 15 items on health issues, positive well-being, hepatitis-specific health issues and hepatitis-specific limitations). The 36 items of the SF-36 are combined into a physical component summary (PCS) score and a mental component summary (MCS) score. The evaluation using the responder analysis for the percentage of patients with an improvement by at least 15% of the scale range at week 48 is used for the benefit assessment.

Statistically significant differences between the treatment arms were observed for neither the summary scores nor the hepatitis-specific domains.

Side effects

In the MYR301 study, adverse events (AEs) occurred in 83.7% (bulevirtide) and 80.4% (best supportive care) of the study participants. No statistically significant differences between the treatment arms were observed for the endpoints of severe adverse events and serious adverse events (SAEs) respectively. AEs leading to discontinuation of the study medication did not occur in the study.

A symptomatic increase in bile salts would be patient-relevant in the present therapeutic indication. In the study, increase in bile salts was collected using the term "bile salts elevated" (PT according to MedDRA). As this does not take into account typical symptoms caused by an increase in bile salts (e.g. itching, headache or nausea), this operationalisation cannot be considered for the assessment.

In detail, the endpoints "general disorders and administration site conditions" and "nervous system disorders" each show a statistically significant effect to the disadvantage of bulevirtide.

Overall assessment

The MYR301 study for the assessment of the safety and efficacy of bulevirtide was submitted for the assessment of the additional benefit. Direct comparator data versus the appropriate comparator therapy are available for the endpoint categories of mortality, morbidity, health-related quality of life and side effects over a treatment period of 48 weeks.

There were no deaths in the MYR301 study.

In the endpoint category of morbidity, there was no statistically significant difference between the treatment arms in the endpoints of liver-related events, fatigue and health status respectively.

The surrogate endpoint of virological response is an endpoint that is significant for assessment of the clinical course of HDV infection and is presented additionally. For the virological response, there was a statistically significant advantage in favour of bulevirtide over best supportive care, based on the component "reduction in viral load by ≥ 2 log_{10}". In contrast,

there was no statistically significant difference between the treatment arms in the component "undetectable HDV-RNA".

In the endpoint category of health-related quality of life, statistically significant differences between the treatment arms were observed for neither the summary scores nor the hepatitis-specific domains in the HQLQ-SF-36 survey of the total population.

In the endpoint category of side effects, there was no statistically significant difference between the treatment arms for severe AEs and SAEs respectively. AEs leading to discontinuation of the study medication did not occur in the study. In detail, the endpoints "general disorders and administration site conditions" and "nervous system disorders" each show a statistically significant disadvantage of bulevirtide. Overall, no relevant differences for the benefit assessment are however derived for the endpoint category of side effects.

In the overall assessment, there were no relevant advantages or disadvantages of bulevirtide over the appropriate comparator therapy for the benefit assessment. An additional benefit is therefore not proven.

b) Children and adolescents 3 to < 18 years of age with chronic hepatitis D infection and compensated liver disease

No data from comparator studies are available for children and adolescents 3 to < 18 years of age with chronic hepatitis D infection and compensated liver disease. In the dossier, the pharmaceutical company argued in favour of transferring the available evidence for adults to children and adolescents, but did not provide any clinical data for this target population that could support transferability.

As part of the written statement procedure, the pharmaceutical company distanced themselves from their position and agree with the assessment that there is inadequate data for evidence transfer and thus for an assessment of the additional benefit.

As a result, it is concluded that the additional benefit of bulevirtide for children and adolescents 3 to < 18 years of age with chronic hepatitis D infection is not proven.

2.1.4 Summary of the assessment

This assessment is the benefit reassessment due to the EUR 30 million turnover limit being exceeded and the assessment of a new therapeutic indication for the active ingredient bulevirtide.

Hepcludex was approved for the treatment of chronic hepatitis delta virus (HDV) infection in adult and paediatric patients aged 3 years and above and weighing at least 10 kg, with compensated liver disease, who have tested positive for HDV RNA in plasma (or serum).

In the therapeutic indication to be considered, 2 patient groups were distinguished:

a) Adults with chronic hepatitis D infection with compensated liver disease,
b) Children and adolescents 3 to < 18 years of age with chronic hepatitis D infection and compensated liver disease.

Patient group a)

The G-BA determined best supportive care as the appropriate comparator therapy.

For this patient group, the pharmaceutical company presented the results of the unblinded MYR301 study. Direct comparator data on bulevirtide versus the appropriate comparator therapy over a treatment period of 48 weeks are available.

No deaths occurred.

In the endpoint category of morbidity, there was no statistically significant difference between the treatment arms in the endpoints of liver-related events, fatigue and health status respectively. The surrogate endpoint of virological response is considered additionally as an endpoint that is significant for assessment of the clinical course of HDV infection. For the virological response, there was a statistically significant advantage in favour of bulevirtide over best supportive care, based on the component "reduction in viral load by ≥ 2 decimal exponents". In contrast, there was no statistically significant difference between the treatment arms in the component "undetectable HDV-RNA".

In the endpoint category of health-related quality of life, there were no statistically significant differences between the treatment arms in the HQLQ-SF-36 survey.

In the endpoint category of side effects, there was no statistically significant difference between the treatment arms for the overall rates of severe AEs and SAEs respectively. AEs leading to discontinuation of the study medication did not occur in the study. In detail, the endpoints "general disorders and administration site conditions" and "nervous system disorders" each show a statistically significant disadvantage of bulevirtide. Overall, no relevant differences for the benefit assessment are however derived for the endpoint category of side effects.

In the overall assessment, there were no relevant advantages or disadvantages of bulevirtide over the appropriate comparator therapy for the benefit assessment. An additional benefit is therefore not proven.

Patient group b)

The G-BA determined best supportive care as the appropriate comparator therapy.

No data from comparator studies are available for this patient group. As a result, it is concluded that the additional benefit of bulevirtide for children and adolescents 3 to < 18 years of age with chronic hepatitis D infection is not proven.

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 information provided by the pharmaceutical company in the benefit assessment dossier (143 to 3,161 patients) is initially used for adult patients. As a basis, the pharmaceutical company took data from Germany on chronic hepatitis B infection, which is subject to uncertainty, particularly due to the survey periods from 2002 to 2013. It can be assumed that the lower limit calculated by the pharmaceutical company is an underestimate due to the significant increase in the sample sizes of subjects with HBV infections since 2015 according to data from the RKI. Based on further literature, the pharmaceutical company calculated the

percentage with chronic HDV co-infection and compensated liver disease, although there are uncertainties regarding the transferability to patients in Germany.

As part of the written statement procedure, the pharmaceutical company submitted new data on the lower limit with 667 patients. This information is not assessable because the calculation method has not been explained. A review conducted by the IQWiG based on data from PharMaAnalyst (https://arzneimittel.wido.de/PharMaAnalyst) for 2024 shows a total of 159,000 defined daily doses (DDD) for Hepcludex. Divided by the number of days, this results in a figure of approximately 434 patients. This figure is used as the lower limit in the present case.

The information provided by the pharmaceutical company in the benefit assessment dossier (0 to 2 patients) is used for children and adolescents 3 to under 18 years of age with chronic HDV infection. The figures are based on data reported by the RKI from 2001 to 2025 and take into account the omission of a potential acute or cured HDV infection and the restriction to patients with compensated liver disease for the lower limit. They are plausible in the order of magnitude.

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 Hepcludex (active ingredient: bulevirtide) at the following publicly accessible link (last access: 14 January 2026):

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

Treatment with bulevirtide should only be initiated and monitored by specialists who are experienced in the treatment of patients with HDV infection.

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 December 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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.

Bulevirtide is administered as monotherapy or in combination with a nucleoside/ nucleotide analogue for the treatment of primary hepatitis B virus (HBV) infection. In patients with chronic HBV/HDV co-infection, the use of peginterferon alfa should be considered for the treatment of HBV infection.

Bulevirtide is dosed for paediatric patients based on body weight, with a minimum dose of 1 mg (for children weighing less than 25 kg) and a maximum dose of 2 mg (for children weighing less than 35 kg). Each 2 mg vial is intended for single use only.

a) Adults with chronic hepatitis D infection and compensated liver disease

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				
Bulevirtide	Continuously, 1 x daily	365	1	365
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care				
Best supportive care	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					
Bulevirtide	2 mg	2 mg	1 x 2 mg	365	365 x 2 mg
Best supportive care		Different from patient to patient			
Appropriate comparator therapy					
Best supportive care					
Best supportive care		Different from patient to patient			

b) Children and adolescents 3 to < 18 years of age with chronic hepatitis D infection and compensated liver disease

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				
Bulevirtide	Continuously, 1 x daily	365	1	365
Best supportive care	Different from patient to patient			
Appropriate comparator therapy				
Best supportive care				
Best supportive care	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					
Bulevirtide	1 – 2 mg	1 – 2 mg	1 x 2 mg	365	365 x 2 mg
Best supportive care		Different from patient to patient			
Appropriate comparator therapy					
Best supportive care					
Best supportive care		Different from patient to patient			

a) Adults with chronic hepatitis D infection and compensated liver disease

and

b) Children and adolescents 3 to < 18 years of age with chronic hepatitis D infection and compensated liver disease

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					
Bulevirtide 2 mg	30 PSI	€ 5,981.31	€ 1.77	€ 0.00	€ 5,979.54
Abbreviation: PSI = powder for solution for injection;					

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 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:

a) Adults with chronic hepatitis D infection with compensated liver disease

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

References:
Product information for bulevirtide (Hepcludex); Hepcludex 2 mg powder for solution for injection; last revised: September 2025

b) Children and adolescents 3 to < 18 years of age with chronic hepatitis D infection and compensated liver disease

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

References:
Product information for bulevirtide (Hepcludex); Hepcludex 2 mg powder for solution for injection; last revised: September 2025

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 26 August 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 1 September 2025, the pharmaceutical company submitted a dossier for the benefit assessment of bulevirtide to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 6 VerfO.

By letter dated 1 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 bulevirtide.

The dossier assessment by the IQWiG was submitted to the G-BA on 27 November 2025, and the written statement procedure was initiated with publication on the G-BA website on 1 December 2025. The deadline for submitting written statements was 22 December 2025.

The oral hearing was held on 12 January 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 10 February 2026, and the draft resolution was approved.

At their session on 19 February 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	26 August 2025	Determination of the appropriate comparator therapy
Working group Section 35a	6 January 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	12 January 2026	Conduct of the oral hearing
Working group Section 35a	20 January 2026 3 February 2026	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	10 February 2026	Concluding discussion of the draft resolution
Plenum	19 February 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 19 February 2026

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

Prof. Hecken