Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Bulevirtide (Chronic Hepatitis Delta Virus (HDV) Infection)

of 18 February 2021

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients.

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation in accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy need not be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, Nos. 2 and 3 SGB V in conjunction with Chapter 5, Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT, exceeds € 50 million during the last 12 calendar months. In accordance with Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence in accordance with Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5, Section 6 VerfO and prove the additional benefit compared with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). On the basis of the statutory requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is deemed to have been proven through the grant of marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at its session on 15 March 2012 to the effect that, in the case of orphan drugs, the G-BA initially no longer independently determines an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit provided is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence.

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (*cf* Section 35a, paragraph 1, sentence 12 SGB V). According to Section 35a, paragraph 2 SGB V, the assessment of the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient bulevirtide in accordance with Chapter 5, Section 8, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 September 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, number 1 VerfO on 31 August 2020.

Bulevirtide for the treatment of chronic hepatitis delta virus (HDV) infection is approved as a medicinal product for the treatment of a rare disease under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed by the G-BA on the basis of the approval studies.

The G-BA carried out the benefit assessment and commissioned the IQWiG to assess the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 1 December 2020 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier assessment carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G12-01) prepared by the IQWiG, and the written statements submitted in the written and oral hearing procedure as well as the amendment to the benefit assessment prepared by the G-BA.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for marketing authorisation with regard to their therapeutic relevance (qualitative) according to the criteria laid down in Chapter 5, Section 5, paragraph 7, sentence 1, numbers 1–4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of bulevirtide.

In light of the above and taking into account the written statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product

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 patients with compensated liver disease.

1 General Methods, Version 6.0 dated 5 November 2020. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

Therapeutic indication of the resolution (resolution of 18 February 2021):

See approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

Hint for a non-quantifiable additional benefit because the scientific data basis does not allow quantification.

Justification:

The pharmaceutical company presents results of the MYR202 and MYR203 studies on which the marketing authorisation of bulevirtide is based.

MYR202 is a multi-centre, open-label, randomised Phase II study to investigate the efficacy and safety of three different dosages of bulevirtide (2 mg/d, 5 mg/d, and 10 mg/d) in combination with tenofovir compared with tenofovir monotherapy (245 mg/d tenofovir alafenamide) over 24 weeks (modified ITT population: n = 28 each) in adult patients with chronic hepatitis D infection. No patients over 65 years of age were included. All treatment groups then received tenofovir monotherapy for a further 24 weeks. Only the dosage of 2 mg/d of bulevirtide is compliant with marketing authorisation and is therefore taken into consideration in the present assessment. The combination therapy of bulevirtide with tenofovir corresponds to the marketing authorisation of bulevirtide, which in accordance with the product information (see there, Section 4.2, as of July 2020) is to be administered either as monotherapy or in combination with a nucleoside/nucleotide analogue for the treatment of the basic hepatitis B infection. The comparison of bulevirtide 2 mg/d plus tenofovir vs tenofovir is therefore relevant for the benefit assessment. By agreeing to participate in the pharmacokinetics sub-study, the patient was randomised to one of the intervention arms. Participation in the control arm was thus excluded. For this reason, a random distribution of participants into the treatment arms that actually corresponds to the randomisation principle is no longer possible. A potential bias also arises from changes in the statistical analysis plan made after the last study round. In the baseline characteristics, there are imbalances between the treatment arms (especially in the pre-treatment and HBeAG status). However, there are difficult to interpret because of the small number of cases. Individual observation times were balanced between treatment arms.

MYR203 is also a multi-centre, open-label, randomised Phase II study. In the study phase completed at the time of the benefit assessment, study arms are available to investigate the efficacy and safety of two different dosages of bulevirtide (2 mg/d and 5 mg/d) as monotherapy or in combination with peginterferon-alfa-2a compared with peginterferon-alfa-2a in adult patients with chronic hepatitis D infection (full-analysis-set: n = 15 each). No patients over 65 years of age were included. All patients included were treated for 48 weeks. This was followed by a 24-week follow-up period. Only the dosage of 2 mg/d of bulevirtide is compliant with marketing authorisation and is therefore taken into consideration in the present assessment. The study arm with the bulevirtide/peginterferon-alfa-2a combination therapy does not correspond to a use of bulevirtide that is compliant with the marketing authorisation. The comparison of bulevirtide 2mg/d vs peginterferon-alfa-2a is therefore relevant for the benefit assessment.

Even if bulevirtide monotherapy is eligible in accordance with the marketing authorisation, it remains unclear to what extent the underlying hepatitis B infection should also have been treated in the patients included in the bulevirtide arm. Based on the randomised allocation of patients to the treatment arms, it can be assumed that appropriate treatment would have been indicated. The results of the comparison are therefore subject to uncertainties. There are also uncertainties because of the exploratory approach to conducting the study; here, the extensive protocol changes after the last study rounds in particular must be taken into consideration. By agreeing to participate in the pharmacokinetics sub-study, the patient is randomised to one of the intervention arms. Participation in the control arm is thus excluded. For this reason, a random distribution of participants into the treatment arms that actually corresponds to the

randomisation principle is no longer possible because there is the possibility of an active decision for allocation to one of the three intervention arms. In the baseline characteristics, there are imbalances between the treatment arms. However, there are difficult to interpret because of the small number of cases. Individual observation times were balanced between treatment arms.

In addition, the pharmaceutical company presents a sub-study of the MYR201 study. Their results are not used for the benefit assessment because the significance is too low because of the small number of cases and the unsuitable comparison of only 24 weeks of bulevirtide therapy (followed by peginterferon monotherapy) with 48 weeks of peginterferon-alfa-2a monotherapy. In addition, the study arm with bulevirtide/peginterferon-alfa-2a combination therapy cannot be considered for the reasons mentioned above.

Mortality

No deaths occurred in either of the studies assessed.

Morbidity

Patient-relevant endpoints in the present therapeutic indication are in particular the development of symptomatic liver fibrosis, liver cirrhosis, or hepatocellular carcinoma. Hepatocellular carcinoma was not surveyed in the studies evaluated, and the operationalisation of the assessment of fibrosis or cirrhosis is not considered adequate because of unclear uniformity in the assessment of liver biopsy findings and different collection times in the MYR203 study.

The virological response is an important endpoint for the assessment of the clinical course and is therefore presented additionally. A validation as a surrogate parameter is not available. In the two studies it was operationalised as a negative HDV RNA PCR test result or a reduction of ≥ $2\log_{10}$ IU/ml at the end of the treatment phase and at the end of the follow-up phase.

The negative test result was achieved in only one patient in the bulevirtide/tenofovir arm of the MYR202 study and in two patients each in the control and verum arms of the MYR203 study at the end of the treatment phase. The results are not statistically significant. Significantly more patients achieved a reduction in HDV RNA of ≥ $2\log_{10}$ IU/ml; here there was a statistically significant difference in favour of bulevirtide/tenofovir (n = 15; 53.6%) compared with tenofovir (n = 1; 3.6%) in the MYR202 study. However, the statistical significance was lost after the follow-up period. This is due to the sharp reduction in responder numbers (from 15 to 2) in the bulevirtide/tenofovir arm during the follow-up period. Similarly, in the MYR203 study, statistical significance was reached after only the follow-up phase because more responders in the bulevirtide arm than in the control arm still met the criterion after the follow-up phase. In both studies, a combined endpoint from both operationalisations was presented. However, this does not result in any additional relevant observations.

In the MYR203 study, virological response was also operationalised as a negative HBV DNA test result; this is also considered in addition for the present assessment. However, there are no significant differences in either the treatment phase or in the follow-up phase.

Quality of life

Health-related quality of life was not surveyed in the studies.

Side effects

In the MYR202 study, there were no statistically significant differences in severe AEs (CTCAE grade ≥ 3), serious AEs, or AEs leading to the discontinuation of the study medication.

In individual AEs with an incidence of more than 10% in at least one treatment arm, there are statistically significant effects in favour (increased alanine aminotransferase (PT)) or to the detriment (nervous system disorders (SOC), infections and infestations (SOC)) of bulevirtide.

Against the background of the non-statistically significant results in the overall rates, no advantage or disadvantage relevant for the benefit assessment can be derived from this.

In the MYR203 study, there were also no statistically significant differences in serious AEs or in AEs that led to the discontinuation of the study medication. In the case of severe AEs (CTCAE grade ≥ 3), there was a statistically significant difference in favour of bulevirtide for the treatment phase but not for the entire study duration, including the follow-up period. At the level of severe AEs with an incidence of more than 5%, the advantage is reflected in the statistically significant effects on blood and lymphatic system disorders (SOC) and neutropenia (PT). In addition, at the level of AEs with an incidence of more than 10%, there are further effects in favour of bulevirtide in both the treatment phase and in the entire study duration. A statistically significant effect to the detriment of bulevirtide was found in the area of SOC investigations (bile acids increased overall, for both the treatment and the entire study phase).

Overall assessment

In the studies presented, there are statistically significant differences in a complementary morbidity endpoint (HDV RNA reduction by ≥ $2\log_{10}$ IU/ml) as well as in the area of individual side effects; however no significant difference is seen in the total number of AEs or SAEs. The results of the MYR203 study suggest a better side-effect profile of bulevirtide compared with peginterferon-alfa-2a. However, because of the small number of cases and the uncertainty described above regarding the appropriateness of bulevirtide monotherapy for the patients in this study, it is not possible to quantify the extent.
In summary, no quantification of the additional benefit of bulevirtide can be derived from the data on morbidity and side effects. Because of the methodological limitations of the studies and the overall limited evidence base, the extent of the additional benefit: for bulevirtide is considered non-quantifiable. On the basis of the submitted data, it is not possible to classify the extent of the effect or the additional benefit into one of the three categories ‘low’, ‘considerable’ or ‘substantial’. An additional benefit does exist, but this is non-quantifiable; at present, with the limited scientific data available, it is impossible to quantify the extent of the additional benefit for patient-relevant endpoints.

Significance of the evidence

The significance of the evidence is limited because of the small number of patients in both studies, the open study design in each case, and the problems with randomisation explained above. The uncertainties mentioned above result in a high risk of bias. Therefore, only a hint for an additional benefit can be derived.

2.1.3 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of bulevirtide has its legal basis in Section 35a, paragraph 3, sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In this 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 pharmaceutical company is obliged to submit to the EMA for review further clinical data on the safety and efficacy of bulevirtide that may be relevant for the assessment of the additional benefit of the medicinal product in accordance with Section 35a SGB V. The limitation enables the timely inclusion of the evidence to be provided to the regulatory authority regarding safety and efficacy in the benefit assessment of the medicinal product according to Section 35a SGB V.

With regard to the evidence to be provided, the EMA requires that a multi-centre, open-label, randomised Phase IIb study and a Phase III study be conducted in order to collect data on efficacy and safety, among other things. The final report of the Phase III study is to be submitted to the EMA on 28 February 2025.

The limitation of this resolution until 1 June 2025 is therefore considered to be appropriate.

Conditions of the limitation:

For the renewed benefit assessment after expiry of the deadline, the results for all patient-relevant endpoints used for the evidence of an additional benefit are to be submitted in the dossier.

In principle, an extension may be granted if it is justified and clearly demonstrated that the period of the limitation is not sufficient.

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, No. 6 VerfO, the procedure for the benefit assessment of bulevirtide shall recommence when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the day of expiry of the deadline to prove the extent of the additional benefit of bulevirtide (Chapter 5, Section 12, No. 1, sentence 2 VerfO).

The possibility that a benefit assessment of bulevirtide can be carried out at an earlier point in time for other reasons (*cf* Section 35a, paragraph 1, sentence 11 SGB V in conjunction with Chapter 5, Section 12 No. 2 VerfO) remains unaffected by this.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of the new medicinal product Hepcludex with the active ingredient bulevirtide.

Hepcludex was approved as an orphan drug under special conditions.

Bulevirtide is approved for the treatment of chronic hepatitis delta virus (HDV) infection in plasma (or serum) HDV-RNA positive adult patients with compensated liver disease.

For the benefit assessment, the multi-centre, open-label, randomised MYR202 and MYR203 Phase II studies submitted by the pharmaceutical company are considered. In the MYR202 study, a combination of bulevirtide with tenofovir versus tenofovir is investigated. In the study arms of the MYR203 study relevant for the assessment, bulevirtide monotherapy was compared with peginterferon alfa-2a.

No deaths occurred in the studies.

There are no assessable data on patient-relevant endpoints in the morbidity category. There are statistically significant differences in a complementary morbidity endpoint (HDV RNA reduction by ≥ $2\log_{10}$ IU/ml) as well as in individual side effects. There is no significant difference in the total number of AE or SAE. The results of the MYR203 study suggest a better side-effect profile of bulevirtide compared with peginterferon-alfa-2a. However, because of the small number of cases and the uncertainty regarding the appropriateness of bulevirtide monotherapy for the patients in this study, it is not possible to quantify the extent.

The health-related quality of life was not surveyed.

In the overall view, there is a non-quantifiable additional benefit.

There are uncertainties because of the open study design and the small number of patients. In addition, randomisation was not guaranteed in some cases because of patients being assigned to a sub-study. The significance of the evidence is therefore classified as a hint.

The resolution is limited until 1 June 2025

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients (approx. 300–4,800) is based on the target population in statutory health insurance. The G-BA bases its resolution on the patient numbers stated by the pharmaceutical company in the dossier. The pharmaceutical company starts from the prevalence data for hepatitis B infection and then uses the prevalence data of the Robert Koch Institute to calculate the HDV proportion for the lower limit of literature data and for the upper limit.

However, the data are subject to great uncertainty with regard to the target population of the therapeutic indication. This is because the restriction to patients with compensated liver disease was not taken into consideration in the calculation. There are also uncertainties because of the limited timeliness of the data and because of the unclear transferability of the population investigated in the sources to the SHI population as a whole and of the incidence data used to the prevalence. In addition, the criterion of HDV RNA detection in accordance with the marketing authorisation was not taken into consideration for the calculation of the HDV proportion but rather an antibody detection in the examined patients.

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: 13 January 2021):

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

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

This medicinal product was approved under “special conditions”. 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 a minimum once per year and update the product information where necessary.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2021).

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 for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

Treatment duration:

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 × daily	365	1	365
Nucleoside/nucleotide analogue				
Adefovir	continuously, 1 × daily	365	1	365
Entecavir	continuously, 1 × daily	365	1	365
Lamivudine	continuously, 1 × daily	365	1	365
Tenofovir alafenamide	continuously, 1 × daily	365	1	365
Tenofovir disoproxil	continuously, 1 × daily	365	1	365

Usage and 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 × 2 mg	365	365 × 2 mg
Nucleoside/nucleotide analogue					
Adefovir	10 mg	10 mg	1 × 10 mg	365	365 × 10 mg
Entecavir	0.5 mg[2] – 1 mg[3]	0.5 mg – 1 mg	1 × 0.5 mg – 1 × 1 mg	365	365 × 0.5 mg – 365 × 1 mg
Lamivudine	100 mg	100 mg	1 × 100 mg	365	365 × 100 mg

2 In accordance with the product information of Baraclude® for nucleoside-naïve adult patients.
3 In accordance with the product information of Baraclude® for lamivudine-refractory adult patients and adult patients with decompensated liver disease.

Designation of the therapy	Dosage/ application	Dose/patient /treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Tenofovir alafenamide	25 mg	25 mg	1 × 25 mg	365	365 × 25 mg
Tenofovir disoproxil	245 mg	245 mg	1 × 245 mg	365	365 × 245 mg

Costs:

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

Costs of the medicinal product:

Designation of the therapy	Package 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 PIJ	€ 14,212.37	€ 1.77	€ 808.40	€ 13,402.20
Adefovir 10 mg	90 TAB	€ 2,015.54	€ 1.77	€ 111.83	€ 1,901.94
Entecavir 0.5 mg[4]	90 FCT	€ 915.54	€ 1.77	€ 71.54	€ 842.23
Entecavir 1 mg[4]	90 FCT	€ 929.88	€ 1.77	€ 72.67	€ 855.44
Lamivudine 100 mg[4]	84 FCT	€ 235.45	€ 1.77	€ 17.75	€ 215.93
Tenofovir alafenamide 25 mg[4]	90 FCT	€ 919.75	€ 1.77	€ 71.87	€ 846.11
Tenofovir disoproxil 245 mg[4]	90 FCT	€ 919.75	€ 1.77	€ 71.87	€ 846.11
Abbreviations: FCT = film-coated tablets; PIJ = powder for the preparation of an injection solution; TAB = tablets					

Pharmaceutical selling price (LAUER-TAXE®) as last revised: 1 February 2021

4 Fixed reimbursement rate

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed 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 standard expenditure in the course of the treatment are not shown.

No additionally required SHI services are taken into account for the cost representation.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

On 31 August 2020, 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, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 December 2020 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 22 December 2020.

The oral hearing was held on 11 January 2021.

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 were discussed at the session of the subcommittee on 9 February 2021, and the proposed resolution was approved.

At its session on 18 February 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	24 November 2020	Information of the benefit assessment of the G-BA
Working group Section 35a	6 January 2021	Information on written statements received; preparation of the oral hearing
Subcommittee on	11 January 2021	Conduct of the oral hearing,

Medicinal Products		
Working group Section 35a	20 January 2021 3 February 2021	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	9 February 2021	Concluding discussion of the draft resolution
Plenum	18 February 2021	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 18 February 2021

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

Prof. Hecken