Gemeinsamer Bundesausschuss

Justification

of 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

Fenfluramine (Dravet syndrome, ≥ 2 years)

of 15 July 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 the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit for an approved orphan drug, although an evaluation of the orphan drug in accordance with the principles laid down in Section 35a paragraph 1, sentence 3, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

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

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

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

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

2. Key points of the resolution

The medicinal product Fintepla, containing the active ingredient fenfluramine, was first placed on the market on 1 February 2021. Relevant date according to Chapter 5, Section 8, paragraph 1, number 7 of the Rules of Procedure of the G-BA (VerfO) for the start of the evaluation procedure for the active ingredient fenfluramine is within three months of the request by the G-BA. If the medicinal product has not yet been placed on the market at that time, the procedure shall start on the date on which it is first placed on the market.

On 5 September 2019, the Federal Joint Committee (G-BA) decided to initiate a benefit assessment for fenfluramine in the indication for the treatment of seizures associated with Dravet syndrome in children aged 2 to 17 years and adults, in accordance with Section 35a (6) SGB V in conjunction with Chapter 5, Section 16 (1) VerfO.

The final dossier was submitted to the G-BA in due time on 1 February 2021. The evaluation process started on the same day.

Fenfluramine for the treatment of seizures associated with Dravet Syndrome as adjunctive therapy to other anti-epileptic medicines approved under Regulation (EC) No 141/2000 of the European Parliament and the Council of 16 December 1999.

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

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate 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 3 May 2021 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G21-06) and the statements made in the written statements and oral hearing process, as well of the addendum drawn up by the G-BA on the benefit assessment.

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

1 General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of fenfluramine (fintepla) in accordance with the product information

Fintepla is indicated for the treatment of seizures associated with Dravet syndrome as an add-on therapy to other anti-epileptic medicines for patients 2 years of age and older.

Therapeutic indication of the resolution (resolution of 15.07.2021):

see approved therapeutic indication

2.1.2 Extend of the additional benefit and significance of the evidence

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

Hint of a considerable additional benefit

Justification:

For the assessment of the additional benefit, the pharmaceutical company submits the results of Study 1 and 1504 studies that justified the marketing authorisation. In addition, the extension study 1503 was used for safety.

Studies 1 and 1504

Study 1 (Studies 1501 and 1502 combined) is a Phase III, randomised, placebo-controlled, double-blind, parallel-group design (1:1:1) study to evaluate the efficacy and safety of fenfluramine 0.7 mg/kg/day and fenfluramine 0.2 mg/kg/day versus placebo in children and adolescents with Dravet Syndrome. For the benefit assessment, only the study arm with fenfluramine 0.7 mg/kg/day and the study arm with placebo are relevant. Randomisation was stratified by age (< 6 vs ≥ 6 years). Study medication was given as adjunctive therapy to existing anti-epileptic therapy, with the use of stiripentol excluded in study 1501 and possible in study 1502. For patients on stiripentol as a basic therapy, the fenfluramine dose was fixed at 0.4 mg/kg/day. The therapy was thus carried out in accordance with the product information. The study's primary outcome measure was the change in the frequency of convulsive seizures from baseline to the titration and maintenance phase.

Study 1504 had a similar design: Patients were randomised 1:1 to 0.4 mg/kg/day fenfluramine and placebo in this study. All study participants received stiripentol as basic therapy. The therapy with fenfluramine was thus carried out in accordance with the product information.

The studies were divided into a 6-week baseline phase, a controlled titration phase (Study 1: Two weeks, study 1504: 3 weeks) and a controlled 12-week maintenance phase. Study participants could subsequently participate in the single-arm extension study 1503. In this case, the maintenance phase was followed by a 2-week transition phase in which therapy was switched to 0.2 mg/kg/day fenfluramine. Unless study participants crossed over to extension study 1503, patients instead underwent a 2-week washout period. For these study participants, a follow-up phase of up to 6 months also followed.

Study 1503

Study 1503 is a single-arm, multicenter, ongoing, open-label Phase III extension study that is eligible to enrol children and adolescents between the ages of 2 and 18 years following the completion of Studies 1501, 1502 and 1504. Stable concomitant medication with at least one anti-epileptic drug existing before the start of the study will be continued. The study's primary objective is to investigate the long-term efficacy and safety of fenfluramine as adjunctive therapy in children and adolescents with Dravet Syndrome. Results of an interim analysis are available.

The study is divided into a 24-month treatment phase (starting with 0.2 mg/kg/day fenfluramine in the first month) and a washout period of up to 2 weeks with a final visit two weeks after early study discontinuation or end of the study. This is followed by a follow-up phase of up to 6 months.

The extension study thus provides findings for the benefit assessment beyond the comparative period of 14 or 15 weeks of the randomised controlled studies. The supplementary consideration of the safety results takes place against the background of the study register on the long-term safety of fenfluramine commissioned in the European public assessment report (EPAR). At the same time, consideration of the extension study to assess efficacy is not necessary due to the low significance of uncontrolled data.

Mortality

There were no deaths in studies 1 and 1504.

Morbidity

Frequency of convulsive and non-convulsive seizures

The number of seizures by type and duration was recorded daily in a diary by the caregiver or the patient. For consistency, the endpoint should always be recorded by the same caregiver who received an introduction to the use of the diary during the screening visit.

Convulsive seizures were grouped as hemiclonic, focal with observable motor signs, generalised tonic-clonic, secondary generalised tonic-clonic, tonic-clonic, and tonic/atonic seizures.

In both studies (Study 1 + 1504), there was a statistically significant difference between study arms in favour of fenfluramine, based on the change in frequency of convulsive seizures between the baseline period and the titration and maintenance phases. As a sensitivity analysis, the group difference in change from baseline was calculated for the maintenance phases and also showed statistically significant differences in favour of fenfluramine in both studies.

In addition to the group differences, responder analyses were used. Here, responders with a reduction in convulsive seizures of ≥ 25, ≥ 50, and ≥ 75 consistently showed statistically significant differences in favour of fenfluramine. These statistically significant advantages were confirmed in the subsequent meta-analyses.

The endpoint increase in the frequency of convulsive seizures > 0% also showed a significant advantage in favour of fenfluramine over placebo, which was also confirmed by a meta-analysis.

In the analysis of the endpoint of change in non-convulsive seizures (focal seizures without a clear motor component, absences or atypical absences, myoclonic seizures, and other unclassified seizures), only those patients who already reported non-convulsive seizures at baseline were included. Thus, this is not the entire subject-compliant sub-population, which limits the significance of the results. There is a statistically significant difference in study 1 but not in study 1504. [

Status epilepticus (supplementary)

"Status epilepticus" was defined as a prolonged epileptic seizure or series of seizures in which the subject did not regain consciousness between ictal events. There are different indications on the duration from which an epileptic seizure was classified as status epilepticus. In addition, status epilepticus was recorded, among other things, as a safety event, which is why it is unclear to what extent an assignment to the category "morbidity" is valid. Overall, it is also unclear to what extent a complete recording of all status epilepticus events took place in the studies. The endpoint is therefore presented as a supplement and located in the presentation of seizure duration.

Hospitalisations (supplementary)

Epilepsy-related hospitalisations were recorded after caregivers were interviewed on the electronic health service utilisation reporting form. In addition, hospitalisations were recorded as part of the safety survey. There is no information on the extent to which the assignment of seizures to hospitalisations was standardised. For the endpoints "status epilepticus" and "serious adverse events", in which hospitalisations were also recorded, hospitalisations were recorded twice, if necessary. It is unclear to what extent these events were separated for the evaluations. Due to the limitations described above, the endpoint is presented as a supplement in the present case.

Clinical General Impression (CGI-I)

The study assessed change in clinical health status using the Clinical Global Impression scale - Improvement (CGI-I) by caregivers.

Despite the subjective assessment by the caregiver, the instrument should be considered in the present therapeutic indication. In principle, the patients' self-assessment of their disease state is to be preferred for the benefit assessment, but in the present disease Dravet Syndrome, it can be assumed that a majority of the patients is not able to do this due to cognitive impairments. The endpoint can therefore be used for this benefit assessment.

There was a statistically significant difference in the proportions of subjects with improvements versus proportions with no changes/worsening between the study arms in favour of fenfluramine in both studies. A meta-analysis confirmed these findings.

Evaluation for deterioration of the overall clinical impression by CGI-I showed no significant difference between the study arms fenfluramine and placebo.

Executive function by means of BRIEF/BRIEF-P

The Behaviour Rating Inventory of Executive Function (BRIEF) is an instrument for assessing executive function in children and adolescents aged 5 to 18 years. Executive functions refer to the control of cognition, emotions and behaviour. The BRIEF is available in three versions: parents, teachers, and self-assessment (from age 11).

The Behaviour Rating Inventory of Executive Function - Preschool Version (BRIEF-P) is a version of the instrument that assesses preschool children aged 2 years to 5 years and 11 months using parent questionnaires.

The instruments BRIEF and BRIEF-P can also be used for the benefit assessment despite the subjective assessment by the caregiver in the present therapeutic indication due to the existing cognitive limitations of the patients.

Regarding BRIEF, only in study 1 a statistically significant difference was found between fenfluramine and placebo in the changes from baseline for the total score and for the underlying indices.

For the total BRIEF-P score, neither Study 1 nor Study 1504 showed statistically significant changes from baseline.

Quality of life

Health-related quality of life was assessed using the Pediatric Quality of Life Inventory 4.0. (PedsQL) questionnaire.

The PedsQL 4.0 measures general health-related quality of life in children and adolescents and consists of four multidimensional scales (Physical Function, Emotional Function, Social Function and School Function) with a total of 23 items and three sum scores: Total score, physical health sum score, psychosocial health sum score. The questionnaire consists of a Likert scale from 1 to 4 (1 = best function [never] to 4 = worst function [always]). The scores are then transformed into a scale of 1 to 100; higher scores indicate a higher quality of life.

The age-appropriate versions for ages 2-4, 5-7, 8-12, and 13-18 years were used in Studies 1 and 1504, with parent/caregiver cross-assessment versions.

The PedsQL is an established and adequately validated generic instrument for assessing the quality of life in pediatric populations with chronic conditions. The endpoint "PedsQL" is considered in the benefit assessment.

Study 1 showed a statistically significant group difference for the total PedsQL score, the clinical relevance of which remains unclear based on Hedges' g. For both study 1504 and the pooled analysis, there was no difference between study arms. Overall, therefore, no difference relevant to the benefit assessment can be identified.

Side effects

There were only minor numerical differences in terms of severe and serious adverse events (AEs) and AEs leading to discontinuation of study medication. With the exception of SAE in study 1504, more events occurred in the verum arm. Effect estimators were not available, so no evaluation is possible. No effect estimators are available for specific side effects either.

With the statement, the pharmaceutical company submitted stratified relative risks on individual study level as well as for the corresponding meta-analyses for the endpoints serious AE and AE of special interest. There were no significant differences between the study arms in the pooled results.

Overall assessment

For the benefit assessment of fenfluramine for the treatment of individuals 2 years of age and older with seizures associated with Dravet Syndrome, results are available from the 14- and 15-week randomised, double-blind, placebo-controlled treatment phases of Study 1 and Study 1504, respectively.

There were no deaths in the studies. For the mortality category, no statement on additional benefit can be derived.

In the morbidity category, a reduction in the frequency of seizures is an important therapeutic goal in the present therapeutic indication and of high clinical relevance. For the clinically relevant endpoints in this therapeutic indication, frequency of convulsive seizures and reduction of convulsive seizures by 75%, 50% and 25%, as well as an increase in the frequency of convulsive seizures above 0%, there was a statistically significant advantage of fenfluramine over placebo in both studies. The results on clinical health status, assessed by the caregiver using CGI-C, support the result: In the fenfluramine arms of both studies, an improvement in health status was noted significantly more often. For the endpoint executive function by BRIEF, there was a statistically significant advantage in Study 1, but not in Study 1504. There were no relevant effects for the other morbidity endpoints relevant for evaluation (non-convulsive seizures, executive function status by means of BRIEF-P). The benefits in the endpoint category morbidity are assessed as considerable overall.

In the quality of life category, there are no statistically significant benefits of fenfluramine overall in the evaluations of the PedsQL questionnaire. In the category of side effects, there were no significant differences in severe AEs and AEs of special interest, and no assessable data were available for serious AEs and treatment discontinuations due to AEs.

In the overall assessment of the available results on the patient-relevant endpoints, the G-BA classifies the extent of the additional benefit of fenfluramine for the treatment of patients aged 2 years and older with seizures associated with Dravet Syndrome, based on the criteria in Section 5, paragraph 8, sentences 1, number 2 in conjunction with Section 5, paragraph 7, sentence 1, number 4 AM-NutzenV as considerable.

Significance of the evidence

This assessment is based on the results of the 14- and 15-week randomised, double-blind, placebo-controlled treatment phases of Studies 1 and 1504, respectively.

The potential risk of bias for both studies is considered low.

Uncertainties arise due to the study duration, which can be assessed as short for the present therapeutic indication, and the small size of the study population, which is insufficient in particular for the conclusive assessment of the safety of fenfluramine with regard to the risk of occurrence of valvular heart disease, pulmonary arterial hypertension and growth disturbances. In addition, the present evaluation is based exclusively on study results for children aged 2 - 18 years. In contrast, results investigating treatment with fenfluramine in adults are not available.

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

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Fintepla with the active ingredient fenfluramine.

Fintepla has been authorised as an orphan drug for the treatment of seizures associated with Dravet Syndrome in patients 2 years of age and older as adjunctive therapy to other anti-epileptic medicines.

For this patient group, the pharmaceutical company presents results of the RCTs Study 1 and Study 1504, in which fenfluramine was compared with placebo.

There were no deaths in the studies

There were statistically significant and relevant benefits of fenfluramine for the frequency of convulsive seizures and the reduction of convulsive seizures by 75%, 50% and 25%, respectively. The results on health status (CGI-C) support the result.

There were no statistically significant overall differences in quality of life (PedsQL questionnaire).

From the endpoint category side effects results, no significant differences can be observed for serious AEs and AEs of special interest.

The significance of the evidence is classified as a 'hint' because no data on adult patients were presented, the duration of the study is short for the present therapeutic indication and the size of the study population is small.

In the overall view, a hint of considerable additional benefit is identified.

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

The information on the number of patients (approx. 450 – 2,450) is based on the target population in statutory health insurance (SHI).

The data follow the representations of the pharmaceutical company and the assessment of IQWiG. Uncertainties exist particularly with regard to the different methodologies used in the identified studies to determine the prevalence range. In addition, there are mathematical and methodological uncertainties in the determination of survival rates. In the case of the lower limit, mortality was taken into account without any existing necessity. Overall, the lower limit can be assumed to be underestimated, while the upper limit is subject to uncertainty.

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 Fintepla (active ingredient: fenfluramine) at the following publicly accessible link (last access: 10 March 2021):

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

Treatment with fenfluramine should only be initiated and monitored by doctors experienced in treating patients with epilepsy.

The European Public Assessment Report (EPAR) states that fenfluramine has not been studied in adults.

In accordance with the European Medicines Agency (EMA) requirements regarding additional measures to risk minimisation, the pharmaceutical company should provide training materials for all healthcare professionals prescribing, dispensing and administering fenfluramine and to patients receiving fenfluramine.

Educational material for healthcare professionals includes guidance on the risk of valvular heart disease, pulmonary arterial hypertension and non-intended use for weight control.

Patient education materials include a guide regarding the risk of valvular heart disease and pulmonary arterial hypertension.

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 June 2021).

In general, initial induction regimens are not taken into account for the cost representation since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

To calculate the consumption of medicinal products to be dosed according to weight, the G-BA generally uses non-indication-specific average weights as a basis. For the bodyweight (BW),

the average weight of the German population from the official representative statistics "Mikrozensus 2017 - Körpermaße der Bevölkerung" is therefore used as a basis. The average body weight of children with 2 to under 3 years of age is 14.1 kg, that of adults (≥ 18 years) is 77.0 kg[2].

The dosage depends on whether the concomitant anti-epileptic therapy includes stiripentol. The maximum daily dose for combination therapy without stiripentol is 26 mg and for combination therapy with stiripentol is 17 mg.

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose potencies, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose potencies as well as the scalability of the respective dosage form. The maximum daily dose was based on the consumption according to the information in the product information.

In the calculation, the shelf life of the medicinal products was taken into account, and, if applicable, the discard due to expiry of the shelf life was included.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ year
Medicinal product to be assessed				
Fenfluramine	Twice daily	365	1	365

Consumption:

Designation of the therapy	Dosage/ application	Dosage/patient/days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Patients not taking stiripentol					
Fenfluramine	0.35 mg/kg = 4.94 mg - 13 mg	9.88 mg - 26 mg	2 x 4.84mg = 2.2 ml - 2 x 13.2 mg = 6 ml	365	730 x 4.84 mg - 730 x 13.2 mg
Patients taking stiripentol					

2 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dosage/patient/days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Fenfluramine	0.2 mg/kg = 2.82 mg - 8.6 mg	5.64 mg - 17 mg	2 x 2.86mg = 1.3 ml - 2 x 8.8 mg = 4 ml	365	730 x 2.86 mg - 730 x 8.8 mg

Costs:

Costs of the medicinal product:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate § 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Fenfluramine	120 ml OS	€ 2,555.41	€ 1.77	€ 142.66	€ 2,410.98
Fenfluramine	360 ml OS	€ 7,551.45	€ 1.77	€ 427.99	€ 7,121.69
Abbreviations: OS = Oral solution					

Last revised LAUER-TAXE®: 15 June 2021

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 standard expenditure in the course of the treatment are not shown.

When using fenfluramine, the cardiac function must be monitored by echocardiography. Echocardiography should be performed prior to treatment to establish a baseline condition. Monitoring by echocardiography should be performed every 6 months for the first 2 years and annually after that.

Designation of therapy	Type of service	Costs/ unit	Number/ patient/ year	Costs/ patient/ year
Fenfluramine	GOP 33022 Duplex-Echocardiography	€ 34.15	1	€ 34.15

3. Bureaucratic costs calculation

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

4. Process sequence

On 1 February 2021, the pharmaceutical company submitted a dossier for the benefit assessment of fenfluramine to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 7 VerfO.

The benefit assessment of the G-BA was published on 3 May 2021 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 25 May 2021.

The oral hearing was held on 8 June 2021.

An amendment to the benefit assessment with a supplementary assessment was submitted on 24 June 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 the 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 6 July 2021, and the draft resolution was approved.

At its session on 15 July 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	27 April 2021	Information of the benefit assessment of the G-BA

Working group Section 35a	2 June 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal product	8 June 2021	Conduct of the oral hearing
Working group Section 35a	16 June 2021 30 June 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 Medicinal product	6 July 2021	Concluding discussion of the draft resolution
Plenum	15 July 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 July 2021

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

Prof. Hecken