Gemeinsamer Bundesausschuss

Justification

of 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
Fenfluramine (new therapeutic indication: Lennox-Gastaut syndrome, add-on therapy, ≥ 2 years)

of 3 August 2023

Contents

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

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5 Section 5, 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 turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

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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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient fenfluramine (Fintepla) was listed for the first time on 1 February 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 24 January 2023, Fintepla 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, 12.12.2008, sentence 7).

Fenfluramine indicated for the treatment of seizures associated with Lennox-Gastaut syndrome in subjects 2 years and older is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

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

On 10 February 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, No.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 fenfluramine with the new therapeutic indication "treatment of seizures associated with Lennox-Gastaut syndrome in subjects 2 years and older" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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 15 May 2023 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 evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G23-03) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

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

1 General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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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 and Lennox-Gastaut 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 3 August 2023):

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

2.1.2 Extent of the additional benefit and significance of the evidence

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

Hint for a considerable additional benefit

Justification:

For the assessment of the additional benefit, the pharmaceutical company submits the results of the label-enabling study ZX008-1601-Part 1. The uncontrolled extension studies ZX008-1601-Part 2 and ZX008-1900 are not included in the benefit assessment because of the availability of the comparator study ZX008-1601-Part 1 (hereafter referred to as 1601 study).

1601 study is a multicentre, randomised, double-blind, phase III, parallel-group (1:1:1) study to evaluate the efficacy and safety of fenfluramine versus placebo in patients with Lennox-Gaustaut syndrome. Subjects aged 2 to 35 years who had at least 8 drop seizures within 4 weeks at the start of the study and were already receiving 1 - 4 antiepileptic medicinal products were enrolled.

As an intervention, the study participants received fenfluramine 0.7 mg/kg/day or fenfluramine 0.2 mg/kg/day. For the benefit assessment, only the study arm with fenfluramine 0.7 mg/kg/day and the study arm with placebo are relevant. The study medication was administered in both arms as an add-on therapy to the existing antiepileptic therapy. Randomisation was stratified by the patients' body weight (< 37.5 kg; ≥ 37.5 kg).

The study was divided into a 4-week baseline phase, a controlled 2-week titration phase, a controlled 12-week maintenance phase and a 2-week phase-out or transition period. This was followed by a 3 to 6-month follow-up phase with a focus on cardiovascular risks. Alternatively, patients could switch to the uncontrolled study ZX008-1601-Part 2 or ZX008-1900 after the maintenance phase.

The primary endpoint was defined as the change in the frequency of drop seizures during the combined titration and maintenance period. Other endpoints included motor and non-motor seizures, status epilepticus, clinical global impression, quality of life and side effects.

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Mortality

In the study 1601-part 1, one death occurred in the intervention group.

Morbidity

Frequency of epileptic seizures

The number of epileptic seizures was recorded daily by type and duration in a diary by the caregiver or the test subject. 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.

For the endpoint "frequency of epileptic seizures", evaluations on drop seizures, motor seizures and non-motor seizures were submitted by the pharmaceutical company.

Motor seizures were grouped as all generalised tonic-clonic (primary and secondary), tonic, atonic, tonic-atonic, clonic and focal seizures associated with observable motor signs, as well as hemiclonic seizures.

In the 1601 study, the change in the frequency of all countable motor seizures (normalised to 28 days) and in the percentage of subjects with a reduction in seizure frequency of > 0%, ≥ 25% and ≥ 50% each showed a statistically significant advantage in favour of fenfluramine over placebo. In the analyses with a response threshold of ≥ 75% and ≥ 100%, no statistically significant difference was found between the observation arms. The non-motor seizures presented included all countable absences, myoclonic seizures, focal seizures without observable motor signs, infantile spasms and epileptic spasms.

There was no statistically significant difference in the change in the frequency of non-motor seizures (normalised to 28 days) between the treatment groups, nor in the percentage of subjects with a reduction in the frequency of non-motor seizures of > 0%, ≥ 25%, ≥ 50%, ≥ 75% and 100%.

Drop seizures are classified as patient-relevant per se, especially because of the serious injuries that can occur as a result of a fall. In the 1601 study, however, not only seizures that led to a fall were recorded as drop seizures, but also seizures that would have led to a fall if the patient's position had been different. As potential falls are classified as irrelevant to the assessment of the endpoint of drop seizures and no separate evaluation of the actual drop seizures was submitted by the pharmaceutical company, the endpoint is not used for this benefit assessment.

Status epilepticus (supplementary)

"Status epilepticus" was defined as a prolonged epileptic seizure or a series of seizures in which the test subjects did not regain consciousness between ictal events. The seizures either had to last longer than 10 minutes according to the seizure diary or status epilepticus had to have been recorded as a serious adverse event (SAE) (seizure ≥ 30 min; > 1x per day or after medical diagnosis).

Given the differences in definitional approaches in guidelines, it is difficult to assess the validity of the minimum duration of seizures of > 10 minutes for status epilepticus classification in the 1601 study. The German S2k guideline[2] recommends that any epileptic seizure lasting longer than 5 minutes should be defined as status epilepticus and subject to acute antiepileptic treatment. Overall, this results in uncertainties as to whether all relevant

2 Rosenow F., Weber J. et al., Status epilepticus in adults, S2k guideline, 2020, in: German Society of Neurology (ed.), Guidelines for Diagnosis and Therapy in Neurology [last accessed: 07.07.2023].
URL: https://register.awmf.org/assets/guidelines/030-079l_S2k_Status_epilepticus_im_Erwachsenenalter_2022-03.pdf

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events could be recorded in the study with this definition. The endpoint is therefore presented additionally.

The resolution was based on the results relating to seizures documented in the seizure diary with a duration > 10 minutes. There were no significant differences between the treatment arms in either the incidence or the change in frequency of these events.

Epilepsy-related hospitalisations

The post hoc analysed endpoint "epilepsy-related hospitalisations" presented in the dossier is not used for the present benefit assessment since the operationalisation does not allow valid statements on the treatment effects of fenfluramine. The evaluation included events from both the RCT and the uncontrolled extension study (1601-Part 2), so that events after switching to fenfluramine were also recorded in the control arm.

Furthermore, the operationalisation due to the consideration of hospitalisations for the adjustment of the study medication or for the exchange of the vagus nerve stimulator as events of an epilepsy-related hospitalisation is assessed as inappropriate.

Clinical Global Impression - Improvement (CGI-I)

Clinical global impression was assessed in the studies by caregivers using the CGI-I scale. 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 Lennox-Gastaut syndrome it can be assumed that a majority of the patients are unable to do this due to cognitive impairments. The endpoint can therefore be used for this benefit assessment.

There was a statistically significant difference to the advantage of fenfluramine in the percentage of subjects with any improvement in CGI-I and with strong or very strong improvement in CGI-I.

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

Executive function by means of BRIEF / BRIEF-A / BRIEF-P

The Behaviour Rating Inventory of Executive Function (BRIEF) is an instrument for assessing executive functions with regard to control of cognition, emotions and behaviour. Depending on the age at the start of the study, the BRIEF, BRIEF-Preschool (BRIEF-P) or BRIEF-Adult (BRIEF-A) versions were used. The questions were answered in each case by caregivers.

The BRIEF is used in children and adolescents aged 6 to 18 years to assess a wide range of neurological conditions. The other two versions of the measurement instrument were used for preschool children aged 2 to 5 years and 11 months (BRIEF-P) and adults aged 19 to 35 years (BRIEF-A), respectively.

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

However, there was no statistically significant difference between fenfluramine and placebo in the change from baseline in any of the measurement tools.

Quality of life

Health-related quality of life was assessed using the Quality of Life in Childhood Epilepsy (QOLCE) questionnaire developed for patients aged 4 to 18 years. In principle, the questionnaire is considered to be a suitable measuring instrument, but there are uncertainties

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as to whether valid results are also achieved with younger children and with subjects over 18 years of age.

While the endpoint (subscales and overall quality of life) is taken into account, the "QOLCE Total Score" is not used to derive the additional benefit due to the unclear operationalisation.

The 1601 study showed no statistically significant differences in quality of life between treatment with fenfluramine and placebo.

Side effects

For the assessed population, there were no statistically significant differences in the evaluation of severe and serious adverse events between the treatment arms in the study.

There was no statistically significant difference in the overall rates of side effects between fenfluramine and placebo. In detail, the analysis of AEs with an incidence of ≥ 10% for SOC "Infections and infestations" and for PT "Reduced appetite" showed a statistically significant disadvantage of fenfluramine compared to placebo.

Overall assessment

For the benefit assessment of fenfluramine for the treatment of subjects 2 years and older with seizures associated with Lennox-Gastaut syndrome, results are available from the 14-week randomised, double-blind and placebo-controlled treatment phases of the 1601 study. The study medication was administered in both arms as an add-on therapy to the existing antiepileptic therapy.

One death occurred in the intervention arm of the study. No statement on the extent of additional benefit can be derived for the mortality category.

In the morbidity category, a reduction in the frequency of seizures is of high clinical relevance in the present therapeutic indication and represents an important therapeutic goal. For the endpoint "motor seizures", there was a statistically significant advantage in favour of fenfluramine over placebo both in the change in the frequency of motor seizures (normalised to 28 days) and in the percentage of subjects with a reduction in seizure frequency of > 0%, ≥ 25% and ≥ 50%. The results on clinical global impression, assessed by the caregiver using CGI-C, support the result. Treatment with fenfluramine showed a statistically significant advantage over placebo for clinical global impression improvement.

In contrast, for the endpoint "non-motor seizures", no statistically significant differences could be observed between the two treatment arms. There was also no statistically significant difference between the two treatment groups in the endpoint "executive function by BRIEF" in any age group. Overall, the advantages shown in the morbidity endpoint category are assessed as considerable in magnitude.

In the quality of life category, the evaluations of the QOLCE questionnaire showed no statistically significant differences between fenfluramine and placebo.

In the category of side effects, there were no statistically significant differences between the two treatment arms for either severe or serious 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 subjects aged 2 years and older with seizures associated with Lennox-Gastaut syndrome, based on the criteria in Section 5, paragraph 8 in conjunction with Section 5, paragraph 7, sentence 1, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) as considerable.

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Significance of the evidence
This assessment is based on the results of the 14-week randomised, double-blind and placebo-controlled treatment phase of the 1601 study.

The risk of bias at the study level is estimated to be low.

Uncertainties arise due to the study duration, which can be assessed as short for the present therapeutic indication. In particular, this is insufficient for the final assessment of the sustainability of the effects as well as the safety of fenfluramine with regard to the risk of growth disorders as well as the occurrence of valvular heart disease and pulmonary arterial hypertension, which were shown under a higher dosage and a different indication.

In the overall assessment, the significance of the evidence is assessed as a hint due to the short study duration of 14 weeks.

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient fenfluramine.

Fintepla was approved as an orphan drug. The therapeutic indication assessed here is as follows: Treatment of patients aged 2 years and older with seizures associated with Lennox-Gastaut syndrome as an add-on therapy to other anti-epileptic medicines.

For this patient group, the pharmaceutical company presents results of the RCT study 1601, in which fenfluramine was compared to placebo over a period of 14 weeks.

One death occurred in the intervention arm of the study.

For the morbidity endpoint "motor seizures", there was a statistically significant advantage of fenfluramine over placebo both in the change in frequency (normalised to 28 days) and in the percentage of subjects with a reduction in seizure frequency of > 0%, ≥ 25% and ≥ 50% respectively. A statistically significant advantage in favour of fenfluramine could also be observed in the endpoint "Clinical Global Impression - Improvement (CGI-I)". Overall, the extent of the advantages shown is assessed as considerable.

For the endpoint category of quality of life, there were no statistically significant differences overall (QOLCE questionnaire) between treatment with fenfluramine and placebo.
For the endpoint category of side effects, there were no statistically significant differences between fenfluramine and placebo for either severe or serious AEs.

The significance of the evidence is classified in the "hint" category as the study duration for the present therapeutic indication is to be regarded as short and the sustainability of the effects as well as long-term effects on the safety of fenfluramine cannot be conclusively assessed, particularly with regard to the risk of the occurrence of cardiovascular side effects.

In the overall assessment, a hint for a considerable additional benefit of fenfluramine is identified.

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 resolution follows the pharmaceutical company's descriptions of the patient numbers in the lower limit, which are, however, subject to uncertainties, and the patient numbers of the resolution on the active ingredient cannabidiol of 15 April 2021 in the upper limit.

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Compared to the previous procedure, there are changes in the patient numbers. More recent figures on the prevalence of the disease lead to a lower limit. However, due to a lack of diagnostic validation in the study used by the pharmaceutical company, this lower limit is subject to uncertainties. The upper limit stated by the pharmaceutical company seems to be underestimated, as older patients and those diagnosed after the age of six were not taken into account. Consequently, the upper limit of the above resolution is a more accurate estimate.

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: 18 April 2023):

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

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

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients.

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. Among other things, this guideline should point out the importance of regular monitoring of heart function by means of echocardiography.

A controlled access programme (CAP) for fenfluramine has been set up, through which only registered doctors experienced in epilepsy therapy may prescribe the medicinal product.

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 July 2023).

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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.

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Fenfluramine	2 x daily	365	1	365

Consumption:

For the calculation of 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[3].

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

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.

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					
Fenfluramine	0.35 mg/kg = 4.94 mg - 13 mg	9.88 mg - 26 mg	2 x 4.94 mg = 2 x 2.2 ml - 2 x 13 mg = 2 x 6 ml	365	730 x 2.2 ml - 730 x 6 ml

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

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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.

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					
Fenfluramine 2.2 mg/ml	360 ml OS	€ 3,025.34	€ 2.00	€ 290.55	€ 2,732.79
Abbreviations: OS = Oral solution					

LAUER-TAXE® last revised: 15 July 2023

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.

When using fenfluramine, the heart function must be monitored by echocardiography. Echocardiography must 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 the therapy	Type of service	Number	Costs/ unit	Costs/ patient/ year
Medicinal product to be assessed				
Fenfluramine	Duplex-echocardiography (GOP 33022)	1	€ 35.28	€ 35.28

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2.5 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 Fenfluramine

According to Section 35a, paragraph 3, sentence 4, the G-BA designates 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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 10 February 2023, 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 2 VerfO.

The benefit assessment of the G-BA was published on 15 May 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 5 June 2023.

The oral hearing was held on 26 June 2023.

An amendment to the benefit assessment with a supplementary assessment of data submitted in the written statement procedure was submitted on 28 June 2023.

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

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umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 25 July 2023, and the proposed resolution was approved.

At its session on 3 August 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	3 May 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	21 June 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	26 June 2023	Conduct of the oral hearing
Working group Section 35a	4 July 2023 18 July 2023	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 products	25 July 2023	Concluding discussion of the draft resolution
Plenum	3 August 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 August 2023

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

Prof. Hecken

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