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 Perampanel (New Therapeutic Indication: Epilepsy, prim. generalised seizures, 7 to <12 years)

of 3 June 2021

Contents

1. Legal basis

According to Section 35a (1) SGB V, the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first submission on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1st approved therapeutic indication,

2nd medical benefits,

3rd additional medical benefit of the medical product in relation to the appropriate comparator therapy

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Costs of therapy for the statutory health insurance,

6th Requirements for a quality-assured application

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA 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 perampanel (Fycompa) was listed for the first time in the Große Deutsche Spezialitäten-Taxe (Lauer-Taxe) on 15 September 2012.

On 10 November 2020, perampanel received marketing authorisation for a new therapeutic indication to be classified as a major type 2 amendment 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 amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 4 December 2020, i.e. at the latest within four weeks after the disclosure, the pharmaceutical company on the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient Perampanel with the new therapeutic indication (Epilepsy, prim. generalised seizures, 7 to <12 years).

The G-BA commissioned IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 March 2021 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. An oral hearing was also held.

The G-BA came to a decision on whether an additional benefit of perampanel compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has assesses the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of perampanel.

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

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

2.1.1 Approved therapeutic indication of perampanel (fycompa) in accordance with the product information

Fycompa (perampanel) is indicated for the adjunctive therapy of

- partial-onset seizures (POS) with or without secondarily generalised seizures in patients from 4 years of age and older.

- primary generalised tonic-clonic (PGTC) seizures in patients from 7 years of age and older with idiopathic generalised epilepsy (IGE).

Therapeutic indication of the resolution (resolution of 3/06/2021):

Fycompa (perampanel) is indicated for the adjunctive therapy of primary generalised tonic-clonic (PGTC) seizures in patients 7 < 12 years of age with idiopathic generalised epilepsy (IGE).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children aged 7 <12 years with idiopathic generalised epilepsy (IGE) and primary generalised tonic-clonic (PGTC) seizures in adjunctive therapy:

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

Appropriate comparator therapy:

A patient-individual adjunctive antiepileptic therapy, if medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance or contraindication is known, under selection of

clobazam, lamotrigine, topiramate, valproic acid[2]

taking into account the baseline and previous therapy(ies) and considering the reason for the change in therapy and any associated side effects.

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. The comparator therapy should preferably be a non-medicinal treatment whose patient-relevant benefit has already been established by the Federal Joint Committee.
4. The comparator therapy should be part of the appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. The active ingredients clobazam, clonazepam, carbamazepine, lamotrigine, phenytoin, phenobarbital, primidone, topiramate and valproic acid are approved in the therapeutic indication.

on 2. A non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication.

on 3. There are no resolutions on an adjunctive therapy for primary generalised tonic-clonic (PGTC) seizures in children aged 4 to 11 years with idiopathic generalised epilepsy (IGE). In the age group 12 years and over, the following resolution is available:

[2] Valproic acid is not regularly considered for the adjunctive treatment of primary generalised tonic-clonic (PGTC) seizures in children 4 to 11 years of age due to potential for liver damage and teratogenicity. However, in the context of patient-individual therapy, additional treatment with valproic acid may be a possible option.

– Resolution on the benefit assessment of medicinal products with new active ingredient perampanel according to Section 35a SGB V of 17 May 2018:

on 4. The generally accepted state of medical knowledge for the indication was established by means of a search for guidelines and systematic reviews of clinical studies. For the additional treatment of primary generalised tonic-clonic seizures in patients aged 7 to < 12 years with idiopathic generalised epilepsy (IGE) the above-mentioned active ingredients are available according to the respective approved therapeutic indication. The evaluation of the available evidence showed that patient-individual antiepileptic adjunctive therapy of the physician's choice is appropriate, depending on the baseline and previous therapy(ies) and taking into account the reason for the change in therapy and any associated side effects, as long as this is medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance and contraindications are known.

In compliance with the marketing authorisation for the adjunctive therapy of primary generalised tonic-clonic (PGTC) seizures in patients aged 7 to < 12 years with idiopathic generalised epilepsy (IGE), the active ingredients clobazam, clonazepam, carbamazepine, lamotrigine, phenytoin, phenobarbital, primidone, topiramate and valproic acid are available. In order to specify the appropriate comparator therapy, the active ingredients with a marketing authorisation in the present therapeutic indication of perampanel are named and listed individually. Evidence does not support the inference of superiority for any of these active ingredients.

The active ingredient valproic acid is not regularly considered for the adjunctive treatment of partial-onset seizures with or without secondary generalisation in children and adolescents aged 7 to <12 years because of potential for liver damage and teratogenicity. However, in the context of patient-individual therapy, additional treatment with valproic acid may be a possible option.

Due to inadequate evidence, the active ingredients clonazepam, carbamazepine, primidone, phenytoin, and phenobarbital are not designated as part of the appropriate comparator therapy.

In distinction to the publication of the appropriate comparative therapy with the benefit assessment, the following sentence was added "taking into account the basic and previous therapy(ies) and considering the reason for the change in therapy as well as any associated side effects". This is an editorial clarification that does not represent a change in the content of the appropriate comparator therapy.

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

2.1.3 Extent and probability of the additional benefit

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

in Children aged 7 to <12 years with idiopathic generalised epilepsy (IGE) and primary generalised tonic-clonic (PGTC) seizures in adjunctive therapy, the additional benefit is not proven.

Justification:

The single-arm studies *E2007-G000-311* and *E2007-G000-232* were submitted for the assessment of the additional benefit of perampanel.

E2007-G000-311 study

Study *E2007-G000-311* examined 180 children with epilepsy aged 4 to < 12 years with partial-onset or generalised seizures who had had at least one partial-onset or primary generalised tonic-clonic seizure in the 12 weeks before the start of the treatment phase despite their previous antiepileptic therapy. Of the 180 children, 25 had epilepsy with primary generalised tonic-clonic seizures and were between 7 to < 12 years of age. After a four-week baseline period, the children received perampanel in addition to their previous antiepileptic therapy. During an 11-week titration phase, the dose of perampanel was gradually increased weekly at two different doses (depending on whether the basic therapy included an enzyme-inducing antiepileptic drug). The administered perampanel dosages deviated from the requirements in the product information because, firstly, the dosage was not weight-adapted according to fixed specifications (< 20 kg, 20 kg < 30 kg and ≥ 30 kg) and, secondly, the intake of enzyme-inducing antiepileptic medicinal product was not taken into account in the titration steps via the amount of the daily dose, but via the time interval between the titration steps. In addition, the initial and maximum doses recommended in the product information for children with enzyme-inducing antiepileptic medicinal product in the basic therapy were exceeded. The titration phase was followed by a 12-week maintenance phase. This was followed by either a four-week follow-up period (without treatment with perampanel) or a switch to a single-arm follow-up study. During the entire course of the study, neither patient-individual dose changes nor the addition or discontinuation of active ingredients were permitted. In addition, the dosages of the previous antiepileptic therapy had to have been stable for at least 4 weeks before the start of the baseline phase. Due to the lack of comparison of perampanel versus the appropriate comparator therapy, the study *E2007-G000-311* cannot be used for the assessment of additional benefit.

E2007-G000-232 study

E2007-G000-232 study examined children aged 2 to <12 years with diagnosed epilepsy regardless of subtype who had at least one seizure in the four weeks prior to the start of the treatment phase despite their previous antiepileptic therapy. Of the 50 study participants, 3 had epilepsy with primary generalised tonic-clonic seizures and were between 7 to < 12 years of age. After a two-week baseline phase, the children received perampanel in addition to their previous antiepileptic therapy. During a 7-week titration phase, the dose of perampanel was gradually increased weekly until the maximum patient-individually tolerated dose was reached in a weight-adapted manner. The administered perampanel dosage deviated from the requirements in the product information, which deviated from the above-mentioned weight ranges per kg body weight. The starting dose in the study is significantly lower than the dose specified in the product information. Furthermore, according to the product information, the dose should only be increased in weekly steps if enzyme-inducing antiepileptic medicinal products are taken at the same time, which was not taken into account here. The titration phase was followed by a four-week maintenance phase. This was followed by either a four-week follow-up period or a switch to a single-arm follow-up study. As in the previously described study, neither patient-individual dose changes nor the addition or discontinuation of active ingredients was permitted during the entire course of the study. Likewise, the dosages of the previous antiepileptic therapy had to have been stable for at least 4 weeks before the start of the baseline phase. Since the study does not provide any data for

a comparison of perampanel with the appropriate comparator therapy and, in addition, the four-week maintenance phase is clearly too short, this study cannot be used for the assessment of the additional benefit either.

Especially in the vulnerable patient population of children aged 7 to < 12 years, comparator data - also to estimate the safety profile - would be desirable.

Even though the marketing authorisation for children aged 7 to < 12 years was granted by the EMA on the basis of an extrapolation of pharmacokinetic/dynamic data, no transfer of an additional benefit from adults to children can be made in the present benefit assessment procedure, because in the benefit assessment resolution of adults (resolution of: 17.5.2018), no additional benefit was identified because no assessable data were available.

The recognition of an additional benefit for children on the basis of results in adults is therefore not possible.

No data were presented versus the appropriate comparator therapy.
An additional benefit of perampanel compared to the appropriate comparator therapy is therefore not proven.

Taking into account the available evidence on the medical benefit of perampanel, the severity of the disease and the opinions of the medical societies on the current reality of care, perampanel may represent a relevant therapeutic option for children aged 7 to <12 years with idiopathic generalised epilepsy and primary generalised tonic-clonic seizures in adjunctive therapy in individual cases.

2.1.4 Summary of the assessment

Two single-arm studies, *E2007-G000-311* and *E2007-G000-232*, on perampanel were submitted as part of the benefit assessment. The *E2007-G000-232* study included only a four-week maintenance phase of perampanel. No data are available for perampanel for adjunctive therapy in children aged 7 to <12 years with idiopathic generalised epilepsy and primary generalised tonic-clonic seizures versus the appropriate comparator therapy (patient-individual adjunctive antiepileptic therapy). An additional benefit is not proven.

Perampanel may be a relevant treatment option for children aged 7 to <12 years with idiopathic generalised epilepsy and primary generalised tonic-clonic seizures in adjunctive therapy in individual cases.

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.

The G-BA bases its decision on the patient numbers stated by IQWiG in the dossier assessment.

Based on the total population of Germany in 2019, the number of children aged 7 to 11 years is 3,695,576[3], assuming a proportion of SHI-insured children of 87.84%[4].

Prevalence was determined based on publications on the prevalence in children with epilepsy[5] and the proportion of children with idiopathic generalised epilepsy[6] and primary generalised seizures[7] [8].

From the data of a secondary analysis by Hamer et al.,[9] it follows that the proportion of children and adolescents with epilepsies receiving combination therapy (i.e. at least two antiepileptic active ingredients) is 41.7%. However, as this proportion is not limited to children with partial-onset epilepsies, but also includes children and adolescents (up to 18 years of age) with other forms of epilepsy, the overall data are 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 Fycompa (active ingredient: perampanel) at the following publicly accessible link (last access: 24 March 2021):
https://www.ema.europa.eu/en/documents/product-information/fycompa-epar-product-information_de.pdf

2.4 Treatment costs

The treatment costs are based on the information of the product information as well as the information in the Lauer-Taxe (status: 15 May 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 patient-individual 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.

Treatment duration:

3 Statistical B. Population: Germany, reference date, age years. 2020.
4 Federal Ministry of Health. Statutory health insurance - key figures and rules of thumb [online]. 2020. URL: https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/Statistiken/GKV/Kennzahlen_Daten/KF2020Bund_Juli_2020.pdf.
5 Camfield P, Camfield C. Incidence, prevalence and aetiology of seizures and epilepsy in children. Epileptic Disord 2015; 17(2): 117-123
6 Jallon P, Latour P. Epidemiology of idiopathic generalised epilepsies. Epilepsia 2005; 46 (Supl 9): 10-14
7 Forsgren L, Beghi E, Öun A et al. The epidemiology of epilepsy in Europe - A systematic review. Eur J Neurol 2005; 12(4): 245-253.
8 Aaberg KM, Surén P, Søraas CL et al. Seizures, syndromes, and etiologies in childhood epilepsy: The International League Against Epilepsy 1981, 1989, and 2017 classifications used in a population-based cohort. Epilepsia 2017; 58(11): 1880-1891
9 Hamer HM, Dodel R, Strzelczyk A et al. Prevalence, utilization, and costs of antiepileptic medicinal products for epilepsy in Germany--a nationwide population-based study in children and adults. J Neurol 2012; 259(11): 2376-2384.

Name of therapy[10]	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/year
Medicinal product to be assessed				
Perampanel OSUS + FCT	Once daily	365	1	365
Appropriate comparator therapy				
Clobazam SUS + TAB	twice daily	365	1	365
Lamotrigine TOS + TAB	1-2 times a day	365	1	365
Topiramate FCT	twice daily	365	1	365
Valproic acid OS + FCT	2 or 4 times a day	365	1	365

Consumption:

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.

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

10 Abbreviations according to IFA GmbH guideline (https://www.ifaffm.de/mandanten/1/documents/02_ifa_anbieter/richtlinien/IFA-Richtlinien_Darreichungsformen.pdf). FCT: Film-coated tablets; OS: Oral solution; SAE: Oral suspension; TAB: Tablets

"Mikrozensus 2017 - Körpermaße der Bevölkerung" is therefore used[11] as a basis. The average body weight of a 7-year-old child is 26.6 kg and 11-year-old child 42.1 kg.

In this particular patient population, it is up to the physician to decide which is the most appropriate dosage form for each patient from 7 years to < 12 years of age, depending on body weight and dose. For this reason, where available, the dosages of both a solid (tablet or hard capsule) and a liquid formulation (solution, suspension or syrup) are shown for each active ingredient.

If more than one treatment mode was indicated in the product information, "twice daily" was calculated for better comprehensibility.

As it is not always possible to achieve the exact calculated dose per day with the commercially available dose strengths, in these cases rounding up or down to the next higher or lower available dose that can be achieved with the commercially available dose strengths as well as the scalability of the respective dosage form.

Name of therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by strength/day of treatment	Treatment days/ patient/ Year	Average annual consumption by strength
Medicinal product to be assessed					
Perampanel OSUS + FCT	4 mg - 8 mg	4 mg - 8 mg	1 x 4 mg- 1 x 8 mg	365	365 x 4 mg - 365 x 8 mg
Appropriate comparator therapy					
Clobazam SUS	7.98 mg - 42.1 mg	0.3 mg/kg = 7.98 mg - 1 mg/kg = 42.1 mg	Once 8 mg - Once 42 mg	365	2,920 mg - 15,330 mg
Clobazam TAB	7.98 mg - 42.1 mg	0.3 mg/kg = 7.98 mg - 1 mg/kg = 42.1 mg	Once 10 mg - Twice 20 mg	365	365 x 10 mg - 730 x 20 mg
Lamotrigine TOS	13.3 mg -	1 mg/kg = 26.6 mg -	6 x 5 mg -	365	2,190 x 5 mg -

11 Statistisches Bundesamt. Microcensus: questions on health - body measurements of the population 2017 [online]. 2.8.2018 [access: 28/4/2021): URL: www.gbe-bund.de

Name of therapy	Dosage/ Application	Dosage/patient/days of treatment	Usage by strength/day of treatment	Treatment days/ patient/ Year	Average annual consumption by strength
	200 mg	400 mg[12]	Twice 200 mg		730 x 200 mg
Lamotrigine TAB	13.3 mg - 200 mg	1 mg/kg = 26.6 mg - 400 mg[12]	1 x 25 mg- Twice 200 mg	365	365 x 25 mg - 730 x 200 mg
Topiramate FCT 4 to 11 years	66.5 mg - 189.45 mg	5 - 9 mg/kg bw = 133 mg - 378.9 mg	Twice 50 mg - Twice 200 mg	365	730 x 50 mg - 730 x 200 mg
Valproic acid OS 4 to 11 years[13]	399 mg - 631.5 mg	30 mg/kg bw = 798 mg - 1,263 mg	2 x 396.4 mg[14] – 2 x 632.1 mg	365	289,372 mg - 461,433 mg
Valproic acid FCT 4 to 11 years	399 mg - 631.5 mg	30 mg/kg bw = 798 mg - 1,263 mg	Twice 300 mg - Twice 600 mg	365 365	730 x 300 mg - 730 x 600 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 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular strength was first determined on the basis of consumption. Having determined the number of packs of a particular strength, 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 product:

12 The dose range depends on whether valproate and/or inducers of glucuronidation of lamotrigine are also being taken. The upper limit of the range can be used with adjunctive therapy WITHOUT valproate and WITH inducers of glucuronidation of lamotrigine, with a maximum maintenance dose of 400 mg/day.
13 The dosage information refers to sodium valproate. 1 ml of the oral solution is equivalent to 28 drops and contains 300 mg of sodium valproate (corresponding to 260.3 mg of valproic acid).
14 The dosage of 396.4 mg sodium valproate corresponds to 37 drops of the solution.

Name of therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate § 130a SGB V	Cost after deduction of statutory rebates
Medicinal product to be assessed					
Perampanel 0.5 mg/ml	340 ml OSUS	€ 84.62	€ 1.77	€ 4.07	€ 78.78
Perampanel 4 mg	98 FCT	€ 350.36	€ 1.77	€ 18.79	€ 329.80
Perampanel 8 mg	98 FCT	€ 350.36	€ 1.77	€ 18.79	€ 329.80
Appropriate comparator therapy					
Clobazam 2 mg/ml	150 ml OSUS	€ 146.00	€ 1.77	€ 6.41	€ 137.82
Clobazam 10 mg[15]	50 TAB	€ 18.93	€ 1.77	€ 0.00	€ 17.16
Clobazam 20 mg[16]	50 TAB	€ 23.65	€ 1.77	€ 0.00	€ 21.88
Lamotrigine 5 mg[16]	60 TOS	€ 11.29	€ 1.77	€ 0.02	€ 9.50
Lamotrigine 200 mg[16]	100 TOS	€ 40.00	€ 1.77	€ 2.29	€ 35.94
Lamotrigine 25 mg[16]	200 TAB	€ 19.23	€ 1.77	€ 0.65	€ 16.81
Lamotrigine 200 mg[16]	100 TAB	€ 40.00	€ 1.77	€ 2.29	€ 35.94
Topiramate 50 mg[16]	200 FCT	€ 83.40	€ 1.77	€ 5.72	€ 75.91
Topiramate 200 mg[16]	200 FCT	€ 267.56	€ 1.77	€ 20.29	€ 245.50
Valproic acid 300 mg/ml[16]	100 ml OS	€ 22.82	€ 1.77	€ 0.93	€ 20.12
Valproic acid 300 mg[16]	200 FCT	€ 33.92	€ 1.77	€ 1.81	€ 30.34
Valproic acid 600 mg[16]	200 FCT	€ 49.81	€ 1.77	€ 3.07	€ 44.97
Abbreviations: FCT = film-coated tablets; TAB = tablets; TOS = tablets for oral suspension; OSUS = oral suspension					

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Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the

15fixed reimbursement rate

prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucracy cost calculation

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

4. Process sequence

At its session on 25 June 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 04 December 2020, the pharmaceutical company submitted a dossier for the benefit assessment of Perampanel to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 9 December 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient Perampanel.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 March 2021, and the written statement procedure was initiated with publication on the G-BA website on 15 March 2021. The deadline for submitting written statements was 6 April 2021.

The oral hearing was held on 26 April 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 26 May 2021, and the draft resolution was approved.

At its session on 3 June 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	25 June 2019	Determination of the appropriate comparator therapy
Working group Section 35a	21 April 2021	Information on written statement procedures received; preparation of the oral hearing

Subcommittee Medicinal product	26 April 2021	Conduct of the oral hearing,
Working group Section 35a	5 May 2021 19 May 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal product	26 May 2021	Concluding consultation of the draft resolution
Plenum	3 June 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

The matter was discussed in the Working Group on Section 35a on 19 May 2021 and in the Subcommittee on Medicinal Products on 26 May 2021, and a corresponding resolution recommendation was prepared for the plenary.

At its session on 3 June 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Berlin, 3 June 2021

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

Prof. Hecken