Justification

Gemeinsamer Bundesausschuss

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

of 19 December 2019

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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. 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 placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. 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 shall pass a resolution 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 containing the active ingredient vigabatrin is considered to be a new active ingredient within the meaning of Section 35a, paragraph 1 SGB V in conjunction with Chapter 5, Section 2, paragraph 1, sentence, 3. No, 2, of the VerfO because in accordance with Article 38, paragraph 1 of Regulation (EC) No 1901/2006 – Regulation on Medicinal Products for Paediatric Use – authorisation for the paediatric use has been granted in accordance with Articles 5 to 15 of Regulation (EC) Number 726/2004.

The relevant date for the first placing on the market of the medicinal product with the active ingredient vigabatrin in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 July 2019.

In a letter dated 19 December 2017, the pharmaceutical company was requested to submit a complete dossier on the active ingredient vigabatrin in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 of the Rules of Procedure (VerfO) of the G-BA.

The pharmaceutical company did not submit a complete dossier at the relevant time according to Chapter 5, Section 8, paragraph 1 in conjunction with Section 11, paragraph 1, sentence 1 VerfO.

The pharmaceutical company has therefore not submitted the necessary evidence for the benefit assessment according to Section 35a SGB V to the G-BA at the relevant time despite being requested to do so. The legal consequence of Section 35a, paragraph 1, sentence 5 SGB V is that an additional benefit is not proven.

In its benefit assessment, the G-BA made findings on the appropriate comparator therapy, the number of patients in the target population, the requirements for a quality-assured application, and treatment costs. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 1 October 2019, thus initiating the written statement procedure.

In addition, an oral hearing was held.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at 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 vigabatrin (Kigabeq®) in accordance with the product information

Kigabeq is indicated in infants and children from 1 month to less than 7 years of age:

- for treatment in combination with other anti-epileptic medicinal products for patients with resistant partial epilepsy (focal onset seizures) with or without secondary generalisation, that is where all other appropriate medicinal product combinations have proved inadequate or have not been tolerated.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Infants and children from 1 month to less than 7 years of age with resistant partial epilepsy (focal onset seizures) with or without secondary generalisation in whom all other appropriate medicinal product combinations have proved inadequate or have not been tolerated.

Appropriate comparator therapy:

A patient-individual optimisation of the anti-epileptic therapy taking into account the previous therapy.

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 according to 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. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

On 1. The following active ingredients are approved for this indication: Brivaracetam, carbamazepine, clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, primidone, topiramate, valproic acid, vigabatrin, and zonisamide.

On 2. A non-medicinal treatment is not regularly considered in the present therapeutic indication and is therefore not determined as an appropriate comparator therapy.

On 3. No resolutions of the G-BA have been made in the relevant therapeutic indication.

On 4. The general state of medical knowledge was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy in accordance with Section 35a SGB V". Overall, the evidence for the present therapeutic indication is limited.

The assessment of the evidence available showed that a patient-individual optimisation of anti-epileptic therapy taking into account the previous therapy is appropriate. The therapy should be carried out at the doctor's discretion, depending on the basic and previous therapy(s) and taking into account the reason for the change of therapy and any side effects that may be associated with it. It must be considered whether pharmacoresistance (in the sense of an insufficient response), intolerance, or contraindication is known.

In consideration of the marketing authorisation for the therapeutic indication combination treatment of focal or partial epileptic seizures (with or without generalisation), the active ingredients already mentioned under 1 (brivaracetam, carbamazepine, clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, primidone, topiramate, valproic acid, and zonisamide) are available.

In addition, the following active ingredients not approved for the indication and used in healthcare as well as in guidelines in addition to the approved alternatives are recommended: pregabalin, perampanel, phenobarbital, eslicarbazepine, tiagabine.

A superiority for one of the above active ingredients cannot be deduced from the evidence. It should also be noted that valproic acid is not regularly considered for the additional treatment of focal seizures with or without secondary generalisation in infants and children from 1 month to less than 7 years of age because of potential liver damage and teratogenicity. However, within the framework of a patient-individual therapy, additional treatment with valproic acid may be a possible option.

A surgical intervention for the treatment of epilepsy (epilepsy surgery) can be considered in patients with therapy-resistant epilepsy and is thus in principle a therapeutic option in the therapeutic indication. Because surgical intervention is ultimately performed in only a small proportion of patients, this option is not regularly considered and is therefore not determined as an appropriate comparator therapy.

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

2.1.3 Extent and probability of the additional benefit

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

Because the required evidence has not been submitted, the additional benefit in relation to the appropriate comparator therapy is considered unproven (Section 35a, paragraph 1, sentence 5 SGB V).

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment for the active ingredient vigabatrin in the therapeutic indication:

“Kigabeq is indicated in infants and children from 1 month to less than 7 years of age:

- for treatment in combination with other anti-epileptic medicinal products for patients with resistant partial epilepsy (focal onset seizures) with or without secondary generalisation, that is where all other appropriate medicinal product combinations have proved inadequate or have not been tolerated”.

In accordance with Article 38, paragraph 1 of Regulation (EC) Number 1901/2006 – Paediatric Regulation, vigabatrin has been granted approval for paediatric use according to Articles 5 to 15 of Regulation (EC) Number 726/2004.
A patient-individual optimisation of the anti-epileptic therapy taking into account the previous therapy was determined by the G-BA as an appropriate comparator therapy.

The pharmaceutical company did not submit a dossier at the relevant time. In accordance with Section 35a, paragraph 1, sentence 5 SGB V, this has the consequence that no assessment is made as to whether or to what extent there is an additional benefit for the active ingredient vigabatrin in the therapeutic indication “Infants and children from 1 month to less than 7 years of age with resistant partial epilepsy (focal onset seizures) with or without secondary generalisation in whom all other appropriate medicinal product combinations have proved inadequate or have not been tolerated” compared with the appropriate comparator therapy. The additional benefit of vigabatrin in relation to the appropriate comparator therapy is not proven.

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

This information on the number of patients concerns the target population in the statutory health insurance.

Two sources are used to calculate the number of epilepsy patients. A review by Forsgren et al (2005) looked at European studies from 1970 to 2003 and estimated the prevalence of active epilepsy in children and adolescents to be 4.5 to 5 per 1000. Another publication (Hamer et al., 2012)[1] – in which diagnostic and prescription data from a database with a sample of 7.2 million German patients around 2009 were evaluated – calculated a prevalence of 5.2 per 1000 children and young people taking anti-convulsant medications. Derived from the sources, the prevalence of active epilepsy is expected to be between 4.5 and 5.2 per 1000 children and adolescents.

[1] Hamer, H. M., Dodel, R., Strzelczyk, A., Balzer-Geldsetzer, M., Reese, J. P., Schoffski, O., et al. 2012. Prevalence, utilisation, and costs of anti-epileptic drugs for epilepsy in Germany--a nationwide population-based study in children and adults. *Journal of Neurology*, 259(11), 2376–84. Epub 2012/05/01.

Based on the prevalence of epilepsy, the proportion of children and adolescents with focal seizures is determined using two sources. Forsgren et al (2005)[1] indicated that focal seizures occur in 42 to 60% of children. Another source (Pfäfflin, 2011)[2] states generalised epilepsy in 50 to 65% of children, which conversely results in focal epilepsy in 35 to 50% of patients. Combining the two sources gives a range of 35 to 60% with focal epilepsy.

A survey of the population in Germany in the indication area (age: 1 month to under 7 years) was carried out using the database of the Federal Health Monitoring[3]. Based on an extraction of the number of 1-month to 6-year-olds from the population of newborns up to 10 years of age in Germany on the cut-off date of 31 December 2018, this results in a population of approx. 5.3 million.

Calculated with the prevalence for focal seizures in childhood as derived above, the patient population in Germany is approx. 8,400 to 16,600 children.

According to the Federal Health Report, 87.7% of the population will have statutory health insurance in 2018. This results in a number of approx. 7,300 to 14,500 patients.

In the overall picture, the calculation of the size of the target population represents an overestimate because according to the product information, vigabatrin is indicated only if all other suitable medicinal product combinations have proven to be insufficient or were not tolerated.

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 Kigabeq® (active ingredient: vigabatrin) at the following publicly accessible link (last access: 25 October 2019):

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

Treatment with vigabatrin should be initiated and monitored only by specialists in epileptology, neurology, or neuropaediatrics.

All patients should receive an ophthalmological consultation before or shortly after starting treatment with vigabatrin.

After the start of treatment and at least every 6 weeks during therapy, the vision should be assessed. The assessment must be continued for 6 to 12 months after discontinuation of therapy.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 December 2019).

[2] Pfäfflin, M. 2011. Epilepsy epidemiology. Epilepsy Information Centre (ize; Informationszentrum Epilepsie) of the German Society for Epileptology [Online]. Available at: http://www.izepilepsie.de/home/showdoc,id,387,aid,4163.html [accessed on: 26 November 2019]

[3] http://www.gbe-bund.de/; cut-off date of data collection: 31 December 2018; accessed on 30 July 2019

It is assumed that one year will be used to calculate the costs for all medicinal products. This does not take into account the fact that treatment may be discontinued earlier because of non-response or intolerance. The discontinuation criteria according to the product information of the individual active ingredients shall be taken into account in the application of the medicinal products.

Treatment duration:

Designation of the therapy[4]	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Vigabatrin TOS	2 × daily	365	1	365
Appropriate comparator therapy				
Brivaracetam OSL + FCT	2 × daily	365	1	365
Carbamazepin SUS (< 1 year)	1 × daily	365	1	365
Carbamazepin SUS (6 years)	3 × daily	365	1	365
Carbamazepin TAB (from 1 year)	1–2 × daily	365	1	365
Carbamazepin TAB (6 years)	3 × daily	365	1	365
Clobazam OS + TAB	1–2 × daily	365	1	365
Gabapentin OSL + HC	3 × daily	365	1	365

[4] Abbreviations in accordance with IFA GmbH guidelines (https://www.ifaffm.de/mandanten/1/documents/02_ifa_anbieter/richtlinien/IFA-Richtlinien_Darreichungsformen.pdf). FCT: film-coated tablets; HC: hard capsules; OSL: oral solution; SIR: syrup: OSP: oral suspension; TAB: tablets; TOS: tablets for preparing an oral suspension; SUS: suspension

Designation of the therapy[4]	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Lacosamide SIR + FCT	2 × daily	365	1	365
Lamotrigine TOS + TAB	1–2 × daily	365	1	365
Levetiracetam OSL	2 × daily	365	1	365
Oxcarbazepin OSP + FCT	2 × daily	365	1	365
Phenytoin TAB	1–2 × daily	365	1	365
Primidone SUS (< 1 year)	2 × daily	365	1	365
Primidone SUS + TAB (6 years)	2–3 × daily	365	1	365
Primidone TAB (2 years)	2 × daily	365	1	365
Topiramate FCT	2 × daily	365	1	365
Valproic acid OSL + FCT	2–4 × daily	365	1	365
Zonisamide HC	1 × daily	365	1	365

Usage and consumption:

In general, initial induction schemes are not taken into account for the cost representation because 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.

In principle, the G-BA does not base the calculation of the consumption of weight-dependent medicinal products to be dispensed on indication-specific average weights. Body weight (BW) is therefore based on the average weight of the German population from the official

representative statistics “Mikrozensus 2017 - Körpermaße der Bevölkerung” [Microcensus 2017 - Body measurements of the population][5]. The average body weight of children under 1 year of age is 7.6 kg. For 1 year olds, it is 11.6 kg, for 2 year olds, it is 14.1 kg, for 3 year olds, it is 16.2 kg, for 4 year olds, it is 18.5 kg, and for 6 year olds, it is 23.6 kg.

In the case of the special patient collective presented here, it is up to the doctor to decide which is the most suitable dosage form for the respective patient from 1 month to < 7 years depending on body weight and dose. For this reason, 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 available).

If the recommended maintenance dose in relation to age is given as a range in the respective product information, the lower and upper limits of the range are calculated here. If several treatment modes were indicated in the product information, “twice daily” was calculated for better comprehensibility.

Because it is not always possible to achieve the exact calculated dose per day with the commercially available potencies, in these cases, the dose is rounded up or down to the next higher or lower available dose that can be achieved with the commercially available dosage strengths and the scalability of the pharmaceutical form concerned.

In the calculation, the shelf life of the medicinal products was taken into account, and any discard after expiry of the shelf life was included.

Designation of the therapy		Dosage/application	Dose/ patient/treatment day	Consumption by potency/treatment day	Annual average consumption according to potency
Medicinal product to be assessed					
Vigabatrin TOS	< 1 year	152 mg	40 mg/kg = 304 mg	3 × 100 mg	1095 × 100 mg
	6 years	500 mg – 750 mg	1 g – 1.5 g	2 × 500 mg – 3 × 500 mg	730 × 500 mg – 1095 × 500 mg
Appropriate comparator therapy					

[5]Statistisches Bundesamt [German Federal Office for statistics]. Microcensus: Fragen zur Gesundheit; Körpermaße der Bevölkerung 2017 [Questions about health; body measurements of the 2017 population] [online]. 2 August 2018 [Accessed: 28 August 2019]. URL: www.gbe-bund.de

Designation of the therapy		Dosage/application	Dose/ patient/treatment day	Consumption by potency/treatment day	Annual average consumption according to potency
Brivaracetam OSL	4 years	9.25 mg – 37 mg	1–4 mg/kg = 18.5 mg – 74 mg	2 × 10 mg – 2 × 37 mg	7,300 mg – 27,010 mg
	6 years	11.8 mg – 47.2 mg	1–4 mg/kg = 23.6 mg – 94.4 mg	2 × 12 mg – 2 × 47 mg	8,760 mg – 34,310 mg
Brivaracetam FCT	4 years	9.25 mg – 37 mg	1–4 mg/kg = 18.5 mg – 74 mg	2 × 10 mg – (2 × 25 mg + 2 × 10 mg)	730 × 10 mg – (730 × 25 mg + 730 × 10 mg)
	6 years	11.8 mg – 47.2 mg	1–4 mg/kg = 23.6 mg – 94.4 mg	2 × 10 mg – 2 × 50 mg	730 × 10 mg – 730 × 50 mg
Carbamazepine SUS	< 1 year	76 mg– 152 mg	10–20 mg/kg = 76–152 mg	1 × 100 mg[6] – 1 × 200 mg	36,500 mg – 73,000 mg
	6 years	78.7– 157.3 mg	10–20 mg/kg = 236– 472 mg	3 × 100 mg – (2 × 200 mg + 1 × 100 mg)	109,500 mg – 182,500 mg
Carbamazepine TAB	1 year	58–116 mg	10–20 mg/kg = 116– 232 mg	1 × 0.5 × 200 mg[7] – 2 × 0.5 × 200 mg	(182.5 × 200 mg) – (365 × 200 mg)
	6 years	78.7– 157.3 mg	10–20 mg/kg = 236–472 mg	3 × 0.5 × 200 mg – (2 × 200 mg + 1 × 0.5 × 200 mg)	547.5 × 200 mg – (912.5 × 200 mg)

[6] 5 ml suspension (= 1 measuring spoons) contains 100 mg of carbamazepine. According to the product information, the lowest dosage is 100 mg of carbamazepine once a day.
[7] Here only 1 × daily administration because the smallest possible dosage with 2 × daily administration would be too high.

Designation of the therapy		Dosage/application	Dose/ patient/treatment day	Consumption by potency/treatment day	Annual average consumption according to potency
Clobazam OSP	< 1 year	0.38 mg	0.1 mg/kg = 0.76 mg	2 × 0.4 mg	292 mg
	6 years	7.08 mg – 23.6 mg	0.3–1.0 mg/kg = 7.08 – 23.6 mg	1 × 7 mg – 1 × 23.6 mg	2,555 mg – 8,614 mg
Clobazam TAB	6 years	7.08 mg – 23.6 mg	0.3–1.0 mg/kg = 7.08 – 23.6 mg	0.5 × 10 mg – 1.25 × 20 mg	182.5 × 10 mg – 456.25 × 20 mg
Gabapentin OSL	6 years	196.67 mg – 275.33 mg	25–35 mg/kg = 590–826 mg	3 × 200 mg – 3 × 275 mg	219,000 mg – 301,125 mg
Gabapentin HC	6 years	196.67 mg – 275.33 mg	25–35 mg/kg = 590–826 mg	6 × 100 mg – (2 × 300 mg + 2 × 100 mg)	2190 × 100 mg – 730 × 300 mg +730 × 100 mg
Lacosamide SIR	4 years	37 mg–111 mg	4–12 mg/kg = 74– 222 mg	2 × 37.5 mg – 2 × 110 mg	27,375 mg – 80,300 mg
	6 years	47.2 mg – 141.6 mg	4–12 mg/kg = 94.4–283.2 mg	2 × 47.5 mg – 2 × 142.5 mg	34,675 mg – 104,025 mg
Lacosamide FCT	4 years	37 mg–111 mg	4–12 mg/kg = 74–222 mg	2 × 50 mg – 2 × 100 mg	730 × 50 mg – 730 × 100 mg

Designation of the therapy		Dosage/application	Dose/ patient/treatment day	Consumption by potency/treatment day	Annual average consumption according to potency
	6 years	47.2 mg – 118 mg	4–10 mg/kg = 94.4–236 mg	2 × 50 mg – (2 × 100 mg)	730 × 50 mg – 730 × 100 mg
Lamotrigine TSE	2 years	7.05 mg – 105.75 mg	1 – 15 mg/kg = 14.1 – 211.5 mg[8]	(2 × 5 mg + 2 × 2 mg) [9] – (2 × 100 mg + 2 × 5 mg)	(730 × 5 mg + 730 × 2 mg) – (730 × 100 mg + 730 × 5 mg)
	6 years	11.8 mg – 177 mg	1 – 15 mg/kg = 23.6 mg – 354 mg[7]	(4 × 5 mg)[6] – (2 × 100 mg + 2 × 50 mg + 2 × 25 mg + 2 × 2 mg)	(1,460 × 5 mg) – (730 × 100 mg+ 730 × 50 mg + 730 × 25 mg + 730 × 2 mg)
Lamotrigine TAB	2 years	14.1 mg – 105.75 mg	1 – 15 mg/kg = 14.1 – 211.5 mg[7]	0.5 x 25 mg[6,10] – 2 × 100 mg	182.5 × 25 mg – 730 × 100 mg

[8] The dose range depends on whether additional valproate and/or inducers of lamotrigine glucuronidation are taken. The upper limit of the range can be used in the adjunctive therapy WITHOUT valproate and WITH inducers of lamotrigine glucuronidation.
[9] If the calculated dose of lamotrigine cannot be given in whole tablets, the next lower dose that can be given in whole tablets shall be given.
[10] Here only 1 × daily administration because the smallest possible dosage with 2 × daily administration would be too high.

Designation of the therapy		Dosage/application	Dose/ patient/treatment day	Consumption by potency/treatment day	Annual average consumption according to potency
	6 years	11.8 mg – 177 mg	1–15 mg/kg = 23.6 – 354 mg[7]	0.5 × 25 mg[6,7] – (2 × 100 mg + 2 × 50 mg +2 × 25 mg)	182.5 × 25 mg – (730 × 100 mg + 730 × 50 mg + 730 × 25 mg)
Levetiracetam OSL	< 1 year	76 mg – 228 mg	20–60 mg/kg = 152 – 456 mg	2 × 75 mg – 2 × 225 mg[11]	54,750 mg – 164,250 mg
	6 years	236 mg – 708 mg	20 – 60 mg/kg = 472 – 1416 mg	2 × 225 mg – 2 × 700 mg[12]	164,250 mg – 511,000 mg
Oxcarbazepine OSP	6 years	354 mg – 542.8 mg	30–46 mg/kg = 708 – 1085.6 mg	2 × 360 mg – 2 × 540 mg[13]	262,800 – 394,200 mg
Oxcarbazepine TAB	6 years	354 mg – 542.8 mg	30–46 mg/kg = 708 – 1,085.6 mg	2 × 300 mg – 2 × 600 mg	730 × 300 mg × 730 × 600 mg
Phenytoin TAB	< 1 year	38 – 60.8 mg	5–8 mg/kg = 38 – 60.8 mg[14]	0.5 × 100 mg	182.5 × 100 mg

[11] A 150 ml bottle contains a scaled application syringe for preparations for ingestion of 3 ml (for up to 300 mg levetiracetam) scaled from 1 ml to 3 ml. In order ensure the most accurate dosage possible, this pack size should be prescribed for infants and toddlers aged 6 months to under 4 years.

[12] A 300 ml bottle contains a scaled application syringe for 10 ml preparations (scaled from 0.5 ml to 10 ml with scaling steps of 0.25 ml each (equivalent to 25 mg).

[13] The suspension contains a concentration of 60 mg/ml. According to the product information, a scaling of 0.5 ml is possible.

[14] According to product information, the dose administered to children under 6 years of age from the 2nd day of treatment should be determined according to the plasma phenytoin concentration. Therefore only the initial dose can be taken as a basis at this point.

Designation of the therapy		Dosage/application	Dose/ patient/treatment day	Consumption by potency/treatment day	Annual average consumption according to potency
	6 years	100 mg	200 mg	2 × 100 mg	730 × 100 mg
Primidone SUS	< 1 year	76 mg	20 mg/kg = 152 mg	2 × 75 mg	54,750 mg
	6 years	236 mg	20 mg/kg = 472 mg	2 × 237.5 mg	164,250 mg
Primidone TAB	2 years	141 mg	20 mg/kg = 282 mg	2 × 0.5 × 250 mg	365 × 250 mg
	6 years	236 mg	20 mg/kg = 472 mg	2 × 250 mg	730 × 250 mg
Topiramate FCT	2 years	35.25 mg – 63.45 mg	5 – 9 mg/kg = 70.5– 126.9 mg	(2 × 0.5 × 50 mg + 2 × 0.5 × 25 mg) – (2 × 0.5 × 100 mg + 2 × 0.5 × 25 mg)	(365 × 50 mg + 365 × 25 mg) – (365 × 100 mg + 365 × 25 mg)
	6 years	59 mg – 106.2 mg	5–9 mg/kg = 118– 212.4 mg	(2 × 50 mg + 2 × 0.5 × 25 mg) – 2 × 100 mg	(730 × 50 mg + 365 × 25 mg) – 730 × 100 mg
Valproic acid OSL	< 1 year	114 mg	30 mg/kg = 228 mg[15]	2 × 111.6 mg[16]	81,468 mg[17]
	6 years	354 mg	30 mg/kg = 708 mg[12]	2 × 353.3 mg[18]	257,909 mg[19]

[15] The dosage information refers to sodium valproate. 1 ml of the solution to be taken corresponds to 28 drops and contains 300 mg of sodium valproate (corresponding to 260.3 mg of valproic acid).
[16] The dosage of 111.6 mg of valproic acid corresponds to 12 drops of the solution.
[17] The total annual dose of 81,468 mg corresponds to 8,760 drops of the solution.
[18] The dosage of 353.3 mg of valproic acid corresponds to 38 drops of the solution.
[19] The total annual dose of 257,909 mg corresponds to 27,740 drops of the solution.

Designation of the therapy		Dosage/application	Dose/ patient/treatment day	Consumption by potency/treatment day	Annual average consumption according to potency
Valproic acid FCT	< 1 year[20]	114 mg	30 mg/kg = 228 mg	2 × 150 mg[21]	730 × 150 mg
	6 years	354 mg	30 mg/kg = 708 mg	2 × 300 mg + 1 × 150 mg	730 × 300 mg + 365 × 150 mg
Zonisamide HC	6 years	141.6 – 188.8 mg	6 – 8 mg/kg = 141.6– 188.8 mg	(1 × 100 mg + 1 × 50 mg) – 2 × 100 mg	(365 × 100 mg + 365 × 50 mg) – 730 × 100 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined 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. If a fixed reimbursement rate is available, this will be used as the basis for the cost calculation.

[20] For children up to 3 years of age, the dosage forms available with a lower active ingredient content (e.g. solution) should preferably be used.

[21] The lowest possible dosage with film-coated tablets when administered twice daily is 300 mg daily. This corresponds to the mean maintenance dose for 1-year-old children.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Vigabatrin 100 mg	100 TOS	€ 128.16	€ 1.77	€ 6.49	€ 119.90
Vigabatrin 500 mg	50 TOS	€ 272.43	€ 1.77	€ 14.48	€ 256.18
Appropriate comparator therapy					
Brivaracetam 10 mg/ml	300 ml OSL	€ 114.16	€ 1.77	€ 5.71	€ 106.68
Brivaracetam 10 mg	14 FCT	€ 35.06	€ 1.77	€ 1.33	€ 31.96
Brivaracetam 25 mg	168 FCT	€ 299.86	€ 1.77	€ 15.99	€ 282.10
Brivaracetam 50 mg	168 FCT	€ 299.86	€ 1.77	€ 15.99	€ 282.10
Carbamazepine 20mg/ml	250 ml SUS	€ 19.19	€ 1.77	€ 1.05	€ 16.37
Carbamazepine 200 mg[22]	200 TAB	€ 23.51	€ 1.77	€ 0.99	€ 20.75
Clobazam 1 mg/ml	150 ml SUE	€ 158.94	€ 1.77	€ 64.20	€ 92.97
Clobazam 2 mg/ml	250 ml SUE	€ 272.00	€ 1.77	€ 33.04	€ 237.19
Clobazam 10 mg[23]	50 TAB	€ 18.87	€ 1.77	€ 0.62	€ 16.48
Clobazam 20 mg[23]	50 TAB	€ 23.59	€ 1.77	€ 1.00	€ 20.82
Gabapentin 50 mg/ml	450 ml OSL	€ 170.96	€ 1.77	€ 8.86	€ 160.33
Gabapentin 100 mg[23]	200 HC	€ 24.78	€ 1.77	€ 1.09	€ 21.92
Gabapentin 300 mg[23]	200 HC	€ 56.60	€ 1.77	€ 3.61	€ 51.22
Lacosamide 10 mg/ml	200 ml SIR	€ 77.55	€ 1.77	€ 3.69	€ 72.09
Lacosamide 50 mg	168 FCT	€ 354.62	€ 1.77	€ 105.70	€ 247.15
Lacosamide 100 mg	168 FCT	€ 462.60	€ 1.77	€ 25.00	€ 435.83
Lamotrigine 2 mg[23]	30 TOS	€ 11.03	€ 1.77	€ 0.00	€ 9.26
Lamotrigine 5 mg[23]	60 TOS	€ 11.33	€ 1.77	€ 0.03	€ 9.53
Lamotrigine 25 mg[23]	42 TOS	€ 12.15	€ 1.77	€ 0.09	€ 10.29
Lamotrigine 50 mg[23]	196 TOS	€ 35.64	€ 1.77	€ 1.95	€ 31.92
Lamotrigine 100 mg[23]	196 TOS	€ 63.82	€ 1.77	€ 4.18	€ 57.87
Lamotrigine 25 mg[23]	200 TAB	€ 22.78	€ 1.77	€ 0.93	€ 20.08
Lamotrigine 50 mg[23]	200 TAB	€ 36.39	€ 1.77	€ 2.01	€ 32.61

[22] Fixed reimbursement rate

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Lamotrigine 100 mg[23]	200 TAB	€ 65.41	€ 1.77	€ 4.30	€ 59.34
Levetiracetam 100 mg/ml[23]	150 ml OSL	€ 67.03	€ 1.77	€ 4.43	€ 60.83
Levetiracetam 100 mg/ml[23]	300 ml OSL	€ 94.43	€ 1.77	€ 6.60	€ 86.06
Oxcarbazepine 60 mg/ml	250 ml SUE	€ 50.71	€ 1.77	€ 5.03	€ 43.91
Oxcarbazepine 300 mg	200 FCT	€ 91.80	€ 1.77	€ 3.84	€ 86.19
Oxcarbazepine 600 mg	200 FCT	€ 171.53	€ 1.77	€ 7.62	€ 162.14
Phenytoin 100 mg[23]	200 TAB	€ 18.74	€ 1.77	€ 0.61	€ 16.36
Primidone 25 mg/ml[23]	250 ml SUS	€ 20.34	€ 1.77	€ 0.00	€ 18.57
Primidone 250 mg[23]	200 TAB	€ 33.95	€ 1.77	€ 1.82	€ 30.36
Topiramate 25 mg[23]	200 FCT	€ 49.42	€ 1.77	€ 3.04	€ 44.61
Topiramate 50 mg[23]	200 FCT	€ 83.34	€ 1.77	€ 5.72	€ 75.85
Topiramate 100 mg[23]	200 FCT	€ 147.23	€ 1.77	€ 10.78	€ 134.68
Valproic acid 300 mg/ml[23]	100 ml OSL	€ 22.76	€ 1.77	€ 0.93	€ 20.06
Valproic acid 150 mg[23]	200 FCT	€ 24.55	€ 1.77	€ 1.07	€ 21.71
Valproic acid 300 mg[23]	200 FCT	€ 33.86	€ 1.77	€ 1.81	€ 30.28
Zonisamide 50 mg[23]	98 HC	€ 121.83	€ 1.77	€ 8.77	€ 111.29
Zonisamide 100 mg[23]	196 HC	€ 315.21	€ 1.77	€ 24.06	€ 289.38
Abbreviations: HC = hard capsules; FCT = film-coated tablets; TAB = tablets; TOS = tablets for preparing an oral suspension					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 December 2019

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.

Because of the risk of visual field defects during therapy with vigabatrin, patients must undergo ophthalmological examinations at regular intervals. Visual field tests (electroretinography or, if possible, perimetry) should be performed at regular 6-month intervals throughout the treatment period. The assessment must be continued for 6 to 12 months after discontinuation of therapy.

In addition, visual investigations should be carried out at least every 6 weeks.

Designation of the therapy	Description of the service	Costs per unit	Number per patient per year	Costs per patient per year
Medicinal product to be assessed				
Vigabatrin	Ophthalmological examination	Non-quantifiable	different	Non-quantifiable

3. Bureaucratic costs

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

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 27 August 2019.

The pharmaceutical company did not submit a dossier for the benefit assessment of vigabatrin to the G-BA in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The G-BA prepared the benefit assessment.

The written statement procedure was initiated with the publication of the benefit assessment prepared by the G-BA on the G-BA website on 1 October 2019. The deadline for submitting written statements was 22 October 2019.

The oral hearing was held on 11 November 2019.

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 10 December 2019, and the proposed resolution was approved.

At its session on 19 December 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	27 August 2019	Determination of the appropriate comparator therapy
Working group Section 35a	5 November 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	11 November 2019	Conduct of the oral hearing
Working group Section 35a	19 November 2019 3 December 2019	Evaluation of the written statement procedure
Subcommittee Medicinal Products	10 December 2019	Concluding discussion of the proposed resolution
Plenum	19 December 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 19 December 2019

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

Prof. Hecken