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 (West's Syndrome)

of 19 December 2019

Contents

1. Legal basis

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

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 who suffer from infantile spasms (West's syndrome)

Appropriate comparator therapy:

Tetracosactide or glucocorticoids (prednisone, prednisolone)

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 the treatment of West's syndrome (BNS spasms): tetracosactide, prednisone, prednisolone, methylprednisolone, clonazepam, nitrazepam, vigabatrin

On 2. An exclusively non-medicinal treatment can not be regularly considered in the present therapeutic indication.

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.

Recommendations for the use of tetracosactide (ACTH), glucocorticoids and vigabatrin can be derived from the current literature. Based on the study situation, none of the medications is generally to be preferred.

Benzodiazepines (clonazepam, nitrazepam) are also approved for the treatment of West's syndrome. However, these should be used only if first-choice medications (ACTH, glucocorticoids, vigabatrin) were ineffective and are therefore not part of the appropriate comparator therapy.

Overall, tetracosactide (ACTH) or glucocorticoids (prednisone, prednisolone) are identified as equally appropriate options. Methylprednisolone is not determined as part of the appropriate comparator therapy because the active ingredient is regularly used only for the initial dosage of glucocorticoid 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 monotherapy of infantile spasms (West's syndrome)".

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".
Tetracosactide or glucocorticoids (prednisone, prednisolone) were determined by the G-BA as appropriate comparator therapies.

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 “Children aged from 1 month to under 7 years who suffer from infantile spasms (West’s syndrome)” 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.

To calculate the number of patients with West’s syndrome, the incidence of the disease was used as a basis because of its early manifestation. This is 2.5 to 6 per 10,000 newborns (Kigabeq - EPAR – Assessment report)[1]. According to the indication, the number of live births within 6 years was calculated. This was based on the birth figures of the Federal Statistical Office between 1 January 2013 and 31 December 2018. During this period, live births in Germany amounted to approximately 4.5 million. At an incidence of 2.5 to 6 per 10,000 newborns, the number of patients aged 0 to 6 years with West’s syndrome is approx. 1125 to 2700. Because the seizures do not usually persist, the number of incidences is considered a sufficient basis for calculating the number of patients.

According to the Federal Health Report, 87.7% of the population had statutory health insurance in 2018. This results in a number of approx. 1000 to 2400 patients.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for 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 a specialist 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).

[1] European Medicines Agency Opinion on the medicinal product https://www.ema.europa.eu/en/documents/assessment-report/kigabeq-epar-public-assessment-report_en.pdf (retrieved on 27 November 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	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/year
Medicinal product to be assessed				
Vigabatrin	2 × daily	730	1	365
Appropriate comparator therapy				
ACTH (tetracosactide)	every 2–8 days	46 – 182.5	1	46 – 182.5
Prednisone	1 × daily	365	1	365
Prednisolone	1 × daily	365	1	365

Usage and consumption:

In principle, the G-BA does base the calculation of the consumption of weight-dependent medicinal products to be dispensed on non-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][2]. The average body weight of children under 1 year of age is 7.6 kg; the average body weight of 6 year olds is 23.6 kg.

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 dose available.

[2] 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	Treatment days/patient/year	Annual average consumption by potency
	Medicinal product to be assessed					
Vigabatrin	< 1 year	190 mg–570 mg	50–150 mg/kg = 380–1140 mg	4 × 100 mg – (2 × 500 mg + 2 × 100 mg)	365	1,460 × 100 mg – (730 × 500 mg + 730 × 100 mg)
	6 years	590 mg – 1,770 mg	50 – 150 mg/kg = 1180–3540 mg	(2 × 500 mg + 2 × 100 mg) – 7 × 500 mg	365	(730 × 500 mg + 730 × 100 mg) – 2.555 × 500 mg
	Appropriate comparator therapy					
ACTH	< 1 year	0,25 mg	0,25 mg	1 injection suspension (1 mg)	46 – 182.5	46 – 182.5 × 1 mg Injection suspension
	6 years	0.25 mg – 1 mg	0.25 mg – 1 mg			
Prednisone	< 1 year	1.9 mg	0.25 mg/kg = 1.9 mg	0.5 × 5 mg	365	182.5 × 5 mg
	6 years	5.9 mg	0.25 mg/kg = 5.9 mg	1 × 5 mg		365 × 5 mg
Prednisolone	< 1 year	1.9 mg	0.25 mg/kg = 1.9 mg	1 × 2 mg	365	365 × 2 mg
	6 years	5.9 mg	0.25 mg/kg = 5.9 mg	1 × 5 mg + 1 × 1 mg		365 × 5 mg + 365 × 1 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.

Designation of the therapy	Package size	Costs (pharmacy wholesale 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					
Tetracosactide 1 mg	10 ISU	€ 204.57	€ 1.77	€ 10.72	€ 192.08
Prednisone 5 mg[3]	100 TAB	€ 16.41	€ 1.77	€ 0.43	€ 14.21
Prednisolone 1 mg[4]	100 TAB	€ 12.47	€ 1.77	€ 0.12	€ 10.58
Prednisolone 2 mg[4]	100 TAB	€ 13.28	€ 1.77	€ 0.00	€ 11.51
Prednisolone 5 mg[4]	100 TAB	€ 15.10	€ 1.77	€ 0.33	€ 13.00
Abbreviations: ISU = injection suspension; 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.

[3] Fixed reimbursement rate

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