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 Cannabidiol (New Therapeutic Indication: seizures associated with tuberous sclerosis, ≥ 2 years, adjunctive therapy)

of 4 November 2021

Contents

1. Legal basis

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

For medicinal products for the treatment of a rare disease (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a paragraph 1, sentence 11, 1st half of the sentence German Social Code, Book Five (SGB V), the additional medical benefit is considered to be proven through the grant of the marketing authorisation 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 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only the extent of the additional benefit is to be quantified, indicating the significance of the evidence.

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

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

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the legal limit of €50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). According to Section 35a paragraph 2 SGB V, the assessment by the G-BA must be

completed within three months of the relevant date for submission of the evidence and published on the internet.

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

2. Key points of the resolution

The relevant date for submission of the combination of active ingredient cannabidiol in accordance with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure of the G-BA (VerfO) is 15 May 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 2 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM- NutzenV) in conjunction with Chapter 2, Section 8, paragraph 1, number 2 VerfO on 14 May 2021.

Cannabidiol for the adjuvant treatment of seizures associated with tuberous sclerosis ≥ 2 years is approved as a medicinal product for the treatment of a rare disease 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 marketing authorisation studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 16 August 2021 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA made its decision on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G12-01) and the statements made in the written statements and oral hearing process, 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 cannabidiol.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of cannabidiol (Epidyolex®) in accordance with the product information

Epidyolex is indicated for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older.

Therapeutic indication of the resolution (resolution of 4 November 2021):

[1] General Methods, version 6.0 from 05.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

See the approved therapeutic indication.

2.1.2 Extent of the additional benefit and significance of the evidence

For cannabidiol in the therapeutic indication of adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older, there is a hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

For the assessment of the additional benefit, the pharmaceutical company submits the results of the double-blinded, placebo-controlled GWEP1521 marketing authorisation studies. The study included patients with tuberous sclerosis aged 1 to 65 years whose seizures were not adequately controlled with current anti-epileptic treatment. There had to be at least 8 TSC-associated seizures within a baseline period of 28 days. Only the study population addressed in the approved therapeutic indication is relevant for the benefit assessment. The marketing authorisation is for patients aged 2 years and older, whereas children aged 1 year were also included in the study. Data on how many children under 2 years of age were included are not available.

Study participants were randomised in a 2:2:1:1 ratio to the two treatment arms with cannabidiol at doses of 25 mg/kg/d and 50 mg/kg/d or to two placebo arms (corresponding to doses of 25 mg/kg/d and 50 mg/kg/d, respectively), with concomitant anti-epileptic medicines maintained stable for at least 4 weeks before screening and stable throughout the blinded study period. The overall characteristics of the randomised study population were balanced between treatment arms.

For the benefit assessment, only the study arm with the dose of 25 mg/kg/d (N = 75) in compliance with the approval and the placebo arms (total N = 76; in each case ITT, identical to the safety population) are relevant; the two placebo arms were combined for the evaluation.

The dosage of 25 mg/kg/d corresponds to the recommended maximum dose according to the marketing authorisation, after which an individual titration of the maintenance dose in the range between 10 and 25 mg/kg/d is carried out under consideration of the individual benefit and risk.

Basically, in the present therapeutic indication, an individual therapy design is required within the scope of the possibilities of the approved dosages under consideration of effect and side effects. Therefore, data on doses of 25 mg/kg/d are relevant for the benefit assessment. However, it must be taken into account in the assessment that the dosage in the study was not titrated individually for each patient. Instead, patients were gradually adjusted by 5 mg per kg every 2 days to the intended dosage (25 mg/kg/d).

The double-blinded study phase included a treatment phase of 16 weeks in total (4-week titration phase plus 12-week maintenance phase).

After completion of the treatment phase, study participants could continue treatment in an open-label extension study. The extension study is not considered in the benefit assessment because it does not include a comparison group, and cannabidiol is used in doses of up to 50 mg/kg/d that are not compliant with the marketing authorisation.

The results of the evaluable patient-relevant endpoints of the study are discussed below.

Mortality

There were no deaths in the study.

Morbidity

Frequency of TSC-associated seizures and other epileptic seizures

Seizures were recorded and classified daily by the patient or caregiver via *Interactive Voice Response System* (IVRS), with appropriate training provided.

For consistency, the recording should always be done by the same person. The seizures were classified into the following types: TSC-associated seizures (focal motor seizures without impairment of consciousness or perception, focal seizures with impairment of consciousness or perception, focal seizures that evolved into bilateral generalised convulsive seizures and generalised seizures [tonic-clonic, tonic-clonic, or atonic]) and other seizures (absences, myoclonic seizures, partial sensory seizures, and infantile or epileptic spasms).

At the end of treatment, cannabidiol showed a statistically significant overall percentage reduction in the frequency of TSC-associated seizures compared at a baseline of 30% compared to placebo. Overall, the frequency of all seizures was also statistically significantly reduced, but the frequency of further seizures was not. In addition to the group differences, responder analyses were used. Responder analyses were performed for the criteria of seizure reduction by at least 25%, 50%, 75%, and 100%, and increase in seizure frequency. Here, for responders with a reduction of ≥ 75% in the frequency of TSC-associated seizures and in the frequency of all seizures, there was a statistically significant advantage for cannabidiol in each case.

Status epilepticus

Status epilepticus, defined as any convulsive or non-convulsive seizure lasting 30 minutes or longer, was also recorded via IVRS and occurred in convulsive and non-convulsive forms in some patients in the study. Statistically significant differences were not observed.

Hospitalisations

Hospitalisations that were considered by the medical investigators to be epilepsy-related were recorded as epilepsy-related hospitalisations. Treatment with cannabidiol resulted in epilepsy-related hospitalisations in 8 study participants and with placebo in one study participant. No statistical evaluation was provided.

Caregiver Global Impression of Change (CGIC) Global Impression of Change (CGIC/SGIC)

The overall impression of health status was assessed in the studies using the Caregiver Global Impression for Change scale (CGI-C). 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 therapeutic indication, it can be assumed that a part of the patients is not able to do this due to cognitive impairments.

A small percentage of study participants (n = 6 of the treatment arm and n = 4 of the placebo arm) also answered the patient-reported version of the Subject Global Impression of Change (SGI-C) instrument.

Due to the small number of cases, the evaluation of the SGI-C as a separate endpoint is not considered significant, but the self-assessment can be taken into account in addition via the combined evaluation of CGI-C and SGI-C. Therefore, for the benefit assessment, the separate CGI-C evaluation is used, and the combined CGI-C/SGI-C evaluation is considered additionally. At the end of the study, there were statistically significantly more patients with an improvement in health status under cannabidiol compared to the placebo arm. The result for the responder criterion "deterioration" at the end of the study was statistically insignificant.

Behaviour

Behavioural and emotional symptoms were recorded using the third-party assessing Achenbach Behavioural Checklists. The two scales for children (Child Behaviour Checklist, CBCL) and the scale for adults (Adult Behaviour Checklist, ABCL) each contain different syndrome scales for internalising, externalising, sleep, and other problems, and a global scale. There are extensive data on reliability and validity but no sufficient data on change sensitivity or clinical relevance thresholds.

For the benefit assessment, those subscales are considered for which a return rate of at least 70% was achieved. None of the subscales or total scores showed a statistically significant difference between the treatment arms in the evaluation of the change in mean value from baseline.

Quality of life

Health-related quality of life was assessed using the Quality of Life in Childhood Epilepsy (QOLCE) questionnaire. The QOLCE is an instrument for measuring the quality of life in children and adolescents between 4 and 18 years of age with epilepsy. The questionnaire consists of 77 items in 5 domains and 16 subscales and is completed by the caregiver. It is considered validated, but no information is available regarding the clinical relevance of change (MID). In the study, data were collected at baseline as well as at the end of treatment. Relevant is the sub-population of study participants under 18 years of age. It is unclear how many results on subjects under 4 years of age were included in the analysis.

Only in the subscale "physical limitations" a statistically significant difference in favour of cannabidiol was found, although irrelevance cannot be excluded when considering the standardised mean differences (per Hedge's *g*). The other subscales, as well as the global scale, show no statistically significant differences in the change from baseline to end of treatment between the treatment groups The return rates for the subscales memory, language, other cognitive abilities, well-being and social interaction were below 70% in both treatment arms so that these subscales cannot be used for the evaluation.

Side effects

In the overall rates of serious adverse events (SAE) and in the treatment discontinuations due to adverse events, statistically significant results to the disadvantage of cannabidiol can be observed.

When considering the AEs with an incidence of ≥ 10%, cannabidiol shows statistically significant differences to the disadvantage of cannabidiol in the system organ class "General disorders and administration site conditions" and in the system organ class "Investigations".

Overall assessment

For the benefit assessment of cannabidiol for the treatment of seizures associated with tuberous sclerosis, data are available on patients treated with the maximum dose of 25 mg/kg/d according to the marketing authorisation.

Results on mortality, morbidity, quality of life and side effects were obtained. There were no deaths in the study. In the category of morbidity, a statistically significant advantage of cannabidiol over placebo (in each case in addition to treatment with other anti-epileptic medicines) was shown for the clinically relevant endpoints in this therapeutic indication: frequency of TSC-associated seizures, frequency of total seizures, and reduction of TSC-associated seizures and reduction of all seizures by 75% in each case. The result on health status, assessed by the caregiver using CGI-C, supports the result: In the cannabidiol arm, an improvement in health status was noted significantly more often. There were no relevant effects for the other morbidity endpoints relevant for evaluation (other seizures, status epilepticus, behaviour).

In the quality of life category, no statistically significant and relevant advantages or disadvantages of cannabidiol result in the evaluations of the QOLCE questionnaire.

In the category of side effects with cannabidiol, there are statistically significant disadvantages in particular in the overall rate of SAE and therapy discontinuations due to AE.

Due to the fixed dosing scheme in the study, with which all study participants are treated with the maximum dose and are not adjusted to an effective dose in the range between 10 and 25 mg/kg/d on a patient-individual basis as defined in the marketing authorisation, the observed effects cannot be conclusively used for an assessment of the extent of the additional benefit.

For the effects observed in the side effects, it can be assumed that the disadvantages of cannabidiol are overestimated due to the maximum dose used. The risk for the occurrence of negative effects can presumably be reduced in the health care context by an individual dose titration defined according to the marketing authorisation, which was not depicted in the study. However, the observed advantages in the morbidity category do not allow a conclusion to be drawn on the actual magnitude of the effect at individual doses, weighing efficacy against tolerability.

Furthermore, it is not possible to estimate a dose-response relationship for this range as no data are available on other doses in the approved dose range, for example, the dose of 10 mg/kg/d.

Overall, there is an additional benefit, which, however, cannot be quantified due to the scientific data basis.

Significance of the evidence

Uncertainties also arise from the fixed titration scheme in the study, which does not reflect the procedure intended according to the marketing authorisation: Instead of a weekly increase of 5 mg/kg/d, the dose increase in the study was made at much shorter intervals of two days each.

In addition, the treatment duration, including the titration phase of 16 weeks, is assessed as rather short for the present therapeutic indication.

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

2.1.3 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the orphan medicinal product Epidyolex with the active ingredient cannabidiol. The therapeutic indication assessed here is as follows:

"Epidyolex is indicated for use as adjunctive therapy of seizures associated with tuberous sclerosis complex (TSC) for patients 2 years of age and older. "

Results of the marketing authorisation study GWEP1521 with patients aged 1 - 65 years are available, in which cannabidiol was compared with placebo, in each case as an add-on to other anti-epileptic medicines. For the benefit assessment, the study arm with the dose of 25 mg/kg/d compliant with marketing authorisation and the combined placebo arms are relevant. No data are available for other dosages in the approved range (10 - 25 mg/kg/d).

There were no deaths in the study. In the morbidity category, a statistically significant advantage of cannabidiol was shown for the clinically relevant endpoints in this therapeutic indication: frequency of TSC-associated seizures, frequency of total seizures, and reduction of TSC-associated seizures and reduction of all seizures by 75% in each case. The result on health status, assessed by the caregiver using CGI-C, supports the result.

In the quality of life category, there are no statistically significant and relevant advantages or disadvantages for cannabidiol

In the category of side effects with cannabidiol, there are statistically significant disadvantages in particular in the overall rate of SAE and therapy discontinuations due to AE.

Due to the fixed dosing scheme in the study, with which all study participants are treated with the maximum dose and are not adjusted to an effective dose in the range 10– 25 mg/kg/d on a patient-individual basis as defined in the marketing authorisation, the presented results cannot be conclusively used for an assessment of the extent of the additional benefit.

Uncertainties also arise from the titration scheme in the study, which does not reflect the procedure according to the marketing authorisation, and the study duration, which can be assessed as short for the present therapeutic indication.

Overall, there is a hint for an additional benefit, which, however, is non-quantifiable due to the scientific data basis.

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

The information on the number of patients (approx. 500 – 2,700) is based on the target population in statutory health insurance (SHI). The data follow the representations of the pharmaceutical company and the assessment of IQWiG.

Uncertainties exist in the transferability of the data determined to the situation in Germany. In addition, it is not taken into account that only patients from the age of 2 years are included in the therapeutic indication. Overall, the upper limit is likely to be overestimated.

The upper limit of 1,727 patients proposed as an alternative by the pharmaceutical company is also considered uncertain and potentially underestimated due to exclusive consideration of outpatient data.

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 Epidyolex (active ingredient: cannabidiol acid at the following publicly accessible link (last access: 29 September 2021):

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

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

A combination of cannabidiol with other anti-epileptic medicines causes pharmacokinetic interactions that can lead to an increase in adverse drug reactions. The patient should be closely monitored for adverse drug reactions. In the case of somnolence or sedation in combination with clobazam, a reduction in the dose of clobazam should be considered.

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 October 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 or patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient or patient//year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Cannabidiol	continuously, 2 x daily	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.

To calculate the consumption of medicinal products to be dosed according to weight, the G-BA generally uses non-indication-specific average weights as a basis. Therefore, for the bodyweight (KG), the average weight of the German population from the official representative statistics "Mikrozensus 2017 - Körpermaße der Bevölkerung"[2] is used as a basis. The average body weight of children from 2 years of age is 14.1 kg, that of adults (≥ 18 years) is 77.0 kg.

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.

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

Designation of the therapy	Dosage/ application	Dose/ patient/ or patient/ treatment days	Usage by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Minimum dosage 2-year-old child					
Cannabidiol (100mg/ml)	70 mg (=5mg/kg)	140 mg	2 x 70 mg	365	6.5 x 100 ml
Maximum dosage adult					
Cannabidiol (100mg/ml)	960 mg (=12.5mg/kg)	1,920 mg (25 mg/kg)	2 x 960 mg	365	70.1 x 100 ml

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 based on the costs per pack after deduction of the statutory rebates.

[2] Federal Statistic Office. Microcensus questions on health - body measurements of the population 2017 [online]. 02.08.2018 [access: 23.02.2021]. URL: www.gbe-bund.de

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					
Cannabidiol (100mg/ml)	100 ml	€ 1,256.39	€ 1.77	€ 0.00	€ 1,254.62

LAUER-TAXE® last revised: 15 October 2021

Costs for additionally required SHI services:

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

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed 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 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. 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 14 May 2021, the pharmaceutical company submitted a dossier for the benefit assessment of cannabidiol to the G-BA in due time in accordance with Chapter 5, Section 8, number 2 VerfO.

The benefit assessment of the G-BA was published on 16 August 2021 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 6 September 2021.

The oral hearing was held on 27 September 2021.

An amendment to the benefit assessment with a supplementary assessment was submitted on 13 October 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 was discussed at the session of the subcommittee on 26 October 2021, and the proposed resolution was approved.

At its session on 4 November 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	10 August 2021	Information of the benefit assessment of the G-BA
Working group Section 35a	21 September 2021	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	27 September 2021	Conduct of the oral hearing
Working group Section 35a	5 October 2021 19 October 2021	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal product	26 October 2021	Concluding discussion of the draft resolution
Plenum	4 November 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 4 November 2021

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

Prof. Hecken