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 Birch Bark Extract (treatment of wounds associated with epidermolysis bullosa (6 months and older))

of 16 February 2023

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

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5, Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

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

Accordingly, at its session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover threshold according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment by the G-BA must be completed within three months of the relevant date for submission of the evidence and published on the internet.

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 online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was 1 September 2022 in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA for the first placing on the (German) market of the active ingredient birch bark extract.

The pharmaceutical company submitted the final dossier to the G-BA 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 VerfO on 31 August 2022.

Birch bark extract indicated for the treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

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

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 1 December 2022 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 resolution 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 G22-30) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA has assessed the studies relevant for the marketing authorisation considering 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 birch bark extract.

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

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Birch bark extract (Filsuvez) in accordance with the product information

Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older.

Therapeutic indication of the resolution (resolution of 16.02.2023):

See therapeutic indication according to marketing authorisation.

2.1.2 Extent of the additional benefit and significance of the evidence

In summary, the additional benefit of birch bark extract is assessed as follows:

For children, adolescents and adults aged 6 months and above with wounds associated with dystrophic and junctional epidermolysis bullosa, there is a hint for a minor additional benefit.

Justification:

For the benefit assessment, the pharmaceutical company presents data from the multicentre, double-blind, randomised, placebo-controlled, pivotal phase III study BEB-13 (hereinafter referred to as the EASE study). 223 patients aged 4 years and above with epidermolysis bullosa (EB), the diagnosed subtypes of dystrophic EB, junctional EB and Kindler EB, and acute EB-associated wounds less than 9 months old with a minimum size of 10 cm^2 and no signs of local infection were enrolled in the study. Patients who received systemic antibiotics 7 days prior to enrolment in the study and topical or systemic corticosteroid therapy 30 days prior to enrolment in the study were excluded.

It was randomised 1:1 to the treatment arm with birch bark extract (N = 109) or the placebo arm with a control gel (N = 114) and stratified by both EB subtype and size of the wound to be treated. The birch bark extract and the control gel were applied at each dressing change but at least every 4 days. The application corresponded to the requirements in the product information. Both EB target wounds and other body sites affected by partial thickness EB wounds were treated. During the study, therapy with topical or systemic antibiotics or corticosteroids was not allowed until the third month.

The primary endpoint included the percentage of subjects with first complete closure of the EB target wound as clinically assessed by the medical investigator within 45 days. In addition, further endpoints on morbidity, health-related quality of life and side effects were assessed.

The study consisted of a 90-day randomised controlled, double-blind period (DBP), followed by a 4-month single-arm open-label follow-up period (OLP). The results of the evaluable patient-relevant endpoints of the DBP are discussed below.

<u>Mortality</u>

Deaths were recorded in the EASE study as part of the safety assessment. No deaths occurred.

Morbidity

Complete wound closure

Due to the genetic disposition in epidermolysis bullosa, the formation of collagen and thus, the connection of the skin layers of the patients is significantly disturbed. Due to this defect, the skin barrier is not fully intact and even minor trauma results in wounds that have a reduced healing rate. Against this background, the complete closure of a wound represents a patient-relevant endpoint in the present therapeutic indication.

The endpoint of wound closure in the EASE study was defined as the first appearance of complete re-epithelialisation without exudate of the predefined EB target wound and refers to the wound status of the EB target wound selected at baseline, based on the target wound criteria (partial thickness wound with a size of 10-50 cm^2 and an age of ≥ 21 days to < 9 months, not located in the anogenital region). All wounds that met the target wound criteria were recorded at baseline with regard to size, location and age in the so-called body chart and photographed according to standardised guidelines.

For the assessment of wound closure, different operationalisations were presented: based on a clinical examination by trained medical investigators, on an assessment of the EB target wound in terms of wound closure or wound size based on photographic documentation by two independent medical investigators, and on the patient's assessment.

Assessment using wound photographs provides a standardised and independent assessment of wound size. Nevertheless, there is uncertainty about the extent to which other aspects of wound healing (including exudate) can be depicted by photographs and assessed with sufficient certainty. Likewise, the patient assessment is subordinate as a clinical assessment is available at the same time. Operationalisation via clinical assessment of the wound is therefore considered the most appropriate assessment of wound closure.

Since the analyses for the endpoint wound closure only show events in the first 45 days, the time until the first complete closure of the target wound according to the clinical assessment is presented additionally.

Confirmation of wound closure was not part of the event definition in the EASE study. This leads to uncertainties in all listed operationalisations of the endpoint of complete wound closure as all events for the first complete wound closure of the target wound up to day 45 were considered, regardless of whether wound closure persisted on day 7 or day 45.

A tipping point analysis of the primary analysis shows that the effect estimate is subject to uncertainty. Depending on the scenario, the result of this endpoint was no longer significant already when one subject was replaced and at the latest when three subjects were replaced. For a large percentage of the wound closures recorded in the primary analysis, no confirmation after 7 days could be documented in the supportive analysis. The risk of bias of this supportive analysis after 7 days is high due to a high percentage of missing values and the clear difference between the groups in the missing values, and the significance of the result is correspondingly limited.

In the endpoint of first complete wound closure of the EB target wound within 45 days according to clinical assessment, there is a statistically significant difference between birch bark extract and placebo. There was no statistically significant difference in the other operationalisations of the endpoint.

Wound status - Change in EB target wound size

The percentage of patients with closed wounds or improved wounds compared to baseline was recorded according to clinical assessment in combination with patient assessment as well as blinded assessment, based on photo documentation, and evaluated post hoc.

Uncertainties remain as it is unclear how the patient self-assessment of wound status was done and which wound characteristics were included in the assessment to improve the wound.

Since there was no difference between the treatment groups in the present endpoint of change in EB target wound size nor in other endpoints such as pain, itching or wound infection, and due to the uncertainties described, the endpoint change in EB target wound size cannot be used to derive an additional benefit regardless of patient relevance and is only presented additionally.

Total wound burden

In the EASE study, the endpoint of Body Surface Area Percentage (BSAP) affected by partial thickness EB wounds was collected to assess total wound burden. The BSAP was collected using a matrix based on the Lund-Browder diagram, which consists of an image of the front and back of the body on which the medical investigators plotted the partial thickness EB wounds. Based on this drawing, so-called regional BSAPs were determined, i.e. the percentage of the body surface area affected by partial thickness EB wounds for the regions head and neck, arms, trunk and legs, and an overall BSAP was calculated.

Since there was no difference between the treatment groups in the present endpoint regarding the percentage of body surface area affected by partial thickness EB wounds, nor in other endpoints such as pain, itching or wound infection, the endpoint regarding the percentage of body surface affected by partial thickness EB wounds cannot be used to derive an additional benefit, irrespective of patient relevance, and is only presented additionally.

In addition, EB activity was submitted using the Epidermolysis Bullosa Disease Activity and Scarring Index (EBDASI) as another measure of total wound burden. The EBDASI consists of a score for disease activity and a score for damage and complications caused by the disease. Only the disease activity score was presented. This depends on the number and size of the lesions present and records the presence of erosions, blistering and crusting on 10 different body regions (ears, face, neck, chest, abdomen, back, arms, hands, legs and feet). Due to uncertainties in validity, the endpoint of EB activity is also not used to derive an additional benefit.

Wound infection

The genetic disposition underlying epidermolysis bullosa causes delayed healing of existing wounds. In this case, the risk of wound infection due to corresponding pathogen infiltration is greatly increased by this prolonged wound healing. Due to the possible serious consequences of wound infections such as sepsis, this endpoint is considered patient-relevant in the present therapeutic indication.

In the EASE study, the endpoint of wound infection was assessed by AE of wound infection or use of topical or systemic antibiotics in association with wound infection, and classified by severity grade.

There was no statistically significant difference between birch bark extract and placebo in the endpoint of wound infection.

Frequency of dressing change

The endpoint of frequency of dressing change was recorded in the EASE study for EB target wounds in the electronic case report form. According to the study protocol, patients should change the dressing at least every 4 days. The evaluation was done post hoc.

There was a statistically significant difference in the endpoint of frequency of dressing change for birch bark extract versus placebo. Due to uncertainties regarding the clinical relevance and absence of any difference between the treatment groups in other endpoints, especially in the endpoint of procedural pain, this endpoint is not used to derive an additional benefit, irrespective of patient relevance, and is only presented additionally.

Pain

The endpoint of pain is generally considered patient-relevant in the therapeutic indication of epidermolysis bullosa. Here, patient relevance is independent of the type of pain, such as pain associated with new or existing wounds (background pain) or pain during dressing changes (procedural pain).

In the EASE study, the endpoints of background pain and procedural pain were assessed for patients aged < 4 years using the Face, Legs, Activity, Cry, Consolability (FLACC) pain rating scale and for patients aged ≥ 4 years using the Wong-Baker FACES pain rating scale. The FLACC score results are shown for day 60, as at day 90 the percentage of subjects in the evaluation for the control arm was <70% and the planned test statistics were not estimable due to the small number of patients in the age group. The results of the Wong-Baker FACES pain scale are shown accordingly for day 90.

The scales selected in the EASE study are assessed as fundamentally suitable instruments for assessing pain characteristics in the present indication in the corresponding age group, even if the Wong-Baker FACES pain rating scale shows limitations in validity, especially when used with young children.

For the endpoints of both background pain and procedural pain, there was no statistically significant difference for birch bark extract versus placebo.

Itching

In the therapeutic indication of epidermolysis bullosa, the activity of the skin due to the continuous occurrence of wounds as well as their healing leads to a strong itching distress for the patients. The occurrence of itching therefore represents a patient-relevant endpoint in the present therapeutic indication.

In the EASE study, the endpoint of itching was assessed using the Itch Man Scale for patients aged 4-13 years and the Leuven Itch Scale for patients aged ≥ 14 years.

The Itch Man Scale involves answering a question about the intensity of itching and associated interference with activities on a 5-point Likert scale. Here, 0 points mean a pleasant feeling without itching and 4 points a very strong itching sensation of the skin, affecting the subject's ability to concentrate.

Within the framework of the Leuven Itch Scale, itching is assessed with regard to the 6 domains of frequency, duration, severity, distress, symptom consequences and symptom localisation related to the last month. The domains of severity and distress are answered on a continuous visual analogue scale (0-100). The scores for the other 4 domains are based on ordinal scales which are transformed to a scale of 0-100.

Both the Itch Man Scale and the Leuven Itch Scale are operationalised in a comprehensible way and appear to be a suitable instrument for recording the endpoint of itching in patients in the present therapeutic indication.

For patients aged 4-13 years, there was a statistically significant change to the advantage of birch bark extract at day 60 using the Itch Man Scale, but this was not confirmed in the evaluation at day 90, nor was it shown in the previous assessment at day 30.

For patients aged 14 years and older, only the subscale "frequency" achieved corresponding return rates at day 90; the other subscales are therefore presented at day 60. Regardless of the time of the assessment, there was no statistically significant difference between the treatment groups.

Overall, there is no statistically significant difference between birch bark extract and placebo for the endpoint of itching.

Sleep impairment

The change in sleep quality is a patient-relevant endpoint in the therapeutic indication of epidermolysis bullosa due to the occurring wound burden and the associated symptoms of itching and pain, which have a negative effect on the sleep quality of the patients.

In the EASE study, patients aged ≥ 14 years were asked if wounds affected their sleep within the last 7 days prior to change of dressing. The assessment was based on an 11-point Likert scale (0 = not at all to 10 = very much).

There was no statistically significant difference between birch bark extract and placebo in the endpoint of sleep impairment.

Quality of life

No usable data regarding quality of life were available.

Side effects

An adverse event (AE) was defined as any poor and unintended event, including a clinically significant abnormal laboratory finding, symptom or disease temporally related to the use of a study medication, whether or not causally related to the study medication. Endpoints that can be assigned to the morbidity category, such as deterioration of the wound status, enlargement of the wound surface, wound infections and reopening of the wound, were also recorded as AEs. The aggregated data submitted by the pharmaceutical company in the context of the written statements, the present operationalisation of the AEs excluding disease-related events is also considered inappropriate for the benefit assessment as a whole. Due to the simultaneous recording of events of the underlying disease, uncertainties remain in the interpretation of results in the category of side effects.

In the evaluations presented on the overall rates of AEs, SAEs, severe AEs and therapy discontinuations due to AEs, there were no statistically significant differences between birch bark extract and placebo.

In the overall assessment, neither advantages nor disadvantages of birch bark extract with regard to side effects were shown, despite remaining uncertainties.

Overall assessment

For the benefit assessment of birch bark extract for the treatment of children, adolescents and adults aged 6 months and older with wounds associated with dystrophic or junctional epidermolysis bullosa (EB), assessable results on mortality, morbidity and side effects are available on the basis of the EASE study.

There were no deaths in the EASE study.

In the morbidity endpoint category, the patient-relevant endpoints of complete wound closure, wound infection, pain, itching and sleep impairment were recorded. There was a statistically significant advantage of birch bark extract for the endpoint of complete wound closure according to clinical assessment. This endpoint is subject to uncertainty due to the uncertainties associated with a tipping point analysis of the primary analysis as well as the persistence of complete wound closure.

No usable data on health-related quality of life are available in the study.

In the evaluations presented on the overall rates of AEs, SAEs, severe AEs and therapy discontinuations due to AEs, there were no statistically significant differences between birch bark extract and placebo. Due to the simultaneous recording of events of the underlying disease, uncertainties remain in the interpretation of results in the category of side effects.

In the overall assessment of the available results, a minor additional benefit of birch bark extract is determined due to the advantage in the endpoint of complete wound closure.

Significance of the evidence

For the EASE study presented, there is a low risk of bias at study level. At the endpoint level, however, the risk of bias is estimated to be high for a large part of the endpoints (especially wound closure, itching, pain, sleep impairment) due to missing values in the evaluation at day 90.

In addition, there are uncertainties in that the EASE study excluded patients who had EB-related wounds older than 9 months. Against this background, it remains unclear whether the limitations of the study population adequately represent the entire therapeutic indication of birch bark extract.

The reliability of data is therefore classified in the category "hint".

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Filsuvez with the active ingredient birch bark extract. Filsuvez was approved as an orphan drug in the following therapeutic indication: "Treatment of partial thickness wounds associated with dystrophic and junctional epidermolysis bullosa (EB) in patients 6 months and older."

For the benefit assessment, the pharmaceutical company presented data from the pivotal, double-blind, randomised, controlled phase III study EASE, which compares birch bark extract with the administration of a control gel.

The endpoint of complete wound closure showed a statistically significant advantage of birch bark extract over placebo. This endpoint is subject to uncertainty due to the uncertainties associated with a tipping point analysis of the primary analysis as well as the persistence of complete wound closure.

No deaths occurred in the study and in the other endpoints in the morbidity category: There was no statistically significant difference between the treatment groups in the endpoints of

wound infection, pain, itching and sleep impairment, and in the endpoints of the side effects category. No usable data regarding the health-related quality of life category were available.

Uncertainties remain in the interpretation of the endpoints of wound closure, itching, pain and sleep impairment due to missing values in the evaluation at day 90 and the exclusion of patients with EB-related wounds older than 9 months.

In the overall assessment, a hint for a minor additional benefit of birch bark extract is identified.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The resolution is based on the information from the dossier assessment of the IQWiG (G22-30).

The G-BA takes into account the patient numbers stated in the pharmaceutical company's dossier, which are, however, subject to overall uncertainties due to the limited epidemiological data basis on the incidence and prevalence of epidermolysis bullosa in the German healthcare context. Overall, the number of patients determined by the pharmaceutical company is largely plausible on the basis of the literature presented.

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 Filsuvez (active ingredient: birch bark extract) at the following publicly accessible link (last access: 1 February 2023):

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

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 February 2023).

Treatment period:

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

The costs for the first year of treatment are shown for the cost representation in the resolution. Since the frequency of treatment depends on the occurrence of corresponding EB wounds as well as the associated individual change of dressing, the usage varies from patient to patient.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Birch bark extract	Different from patient to patient			

Consumption:

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

The dose of the active ingredient birch bark extract depends on the wound surface. According to the product information, the gel should either be applied directly to the wound surface with a thickness of about 1 mm and covered with a sterile, non-adherent wound dressing or applied to the wound dressing in such a way that the gel has direct contact with the wound. The gel should not be applied sparingly.

Due to the variance in size and number of wounds to be treated, the usage based on the dosage instructions varies from patient to patient and cannot be clearly determined.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Birch bark extract	Different from patient to patient				

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					

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
Birch bark extract	30 tubes GEL	€ 10,243.19	€ 2.00	€ 997.20	€ 9243.99
Abbreviations: GEL = gel					

LAUER-TAXE® last revised: 1 February 2023

Costs for additionally required SHI services:

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

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

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.

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with birch bark extract

According to Section 35a, paragraph 3, sentence 4, the Federal Joint Committee shall designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

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

3. Bureaucratic costs calculation

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

4. Process sequence

On 31 August 2022, the pharmaceutical company submitted a dossier for the benefit assessment of birch bark extract to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 1 December 2022 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 22 December 2022.

The oral hearing was held on 9 January 2023.

An amendment to the benefit assessment with a supplementary assessment was submitted on 25 January 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI 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 7 February 2023, and the proposed resolution was approved.

At its session on 16 February 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	22 November 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	4 January 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 January 2023	Conduct of the oral hearing
Working group Section 35a	18 January 2023 1 February 2023	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee Medicinal products	7 February 2023	Concluding discussion of the draft resolution
Plenum	16 February 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 February 2023

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

Prof. Hecken