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 Peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) (new therapeutic indication: peanut allergy, ≥ 1 to < 4 years)

of 3 July 2025

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 all 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 studies 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 the statutory health insurance funds,
6. requirements for a quality-assured application.
7. Number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

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

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

2. Key points of the resolution

The active ingredient peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) (Palforzia) was listed for the first time on 15 October 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 19 December 2024, peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 14 January 2025, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) with the new therapeutic indication

"Palforzia is indicated for the treatment of patients aged 1 to 3 years with a confirmed diagnosis of peanut allergy. Palforzia should be used in conjunction with a peanut-avoidant diet."

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 April 2025 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA have evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts).

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

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

2.1.1 Approved therapeutic indication of Peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) (Palforzia) in accordance with the product information

Palforzia is indicated for the treatment of patients aged 1 to 17 years with a confirmed diagnosis of peanut allergy. Palforzia may be continued in patients 18 years of age and older. Palforzia should be used in conjunction with a peanut-avoidant diet.

Therapeutic indication of the resolution (resolution of 03.07.2025):

Palforzia is indicated for the treatment of patients aged 1 to 3 years with a confirmed diagnosis of peanut allergy. Palforzia should be used in conjunction with a peanut-avoidant diet.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Children aged 1 to 3 years with a confirmed diagnosis of peanut allergy

Appropriate comparator therapy for peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) in conjunction with a peanut-avoidant diet:

- monitoring wait-and-see approach

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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

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

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1. Apart from the active ingredient of peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts), there are currently no medicinal products approved for the treatment of children aged 1 to 3 years with a confirmed diagnosis of peanut allergy.

On 2. A sole non-medicinal treatment cannot be considered in the therapeutic indication.

On 3. No resolutions of the G-BA are available for children aged 1 to 3 years in the therapeutic indication of peanut allergy to be considered here.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V. There are no written statements.

There are only a few methodologically high-quality review papers and guidelines for the treatment of food allergies. Two systematic reviews and the "Managing food allergy" guideline of the Global Allergy and Asthma European Network (GA2LEN) from 2022 could be identified. The guideline recommends offering oral peanut immunotherapy under specialist supervision to children aged 4 years and older with severe, IgE-mediated peanut allergy. The guideline also suggests offering epicutaneous peanut immunotherapy under specialist supervision to children aged 4 to 11 years with severe, IgE-mediated peanut allergy. No specific recommendations are made for children aged 1 to 3 years with a peanut allergy. The current standard of care for this patient group is an allergen-avoidant diet and, if necessary, the use of emergency medication. It is generally assumed that patients will receive medical advice on the measures mentioned. As part of the determination of the appropriate comparator therapy, these measures are defined as the monitoring wait-and-see approach.

Based on the available evidence and in the absence of specific recommendations, the monitoring wait-and-see approach is therefore determined as the appropriate comparator therapy for the treatment of IgE-mediated peanut allergy in this patient population of children aged 1 to 3 years. An allergen-avoidant diet is a prerequisite in all study arms. It is also assumed that the patients in both study arms were informed about the dietary requirements/ recommendations. It is assumed that emergency medication may be used in both study arms in case of accidental exposure and clinical requirement.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) is assessed as follows:

Children aged 1 to 3 years with a confirmed diagnosis of peanut allergy

Hint for a non-quantifiable additional benefit

Justification:

The benefit assessment is based on the randomised, double-blind ARC005 study comparing peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) (in short: peanut protein) versus placebo. A total of 146 children aged 1 to 3 years with sensitisation to peanuts were enrolled. Sensitisation had to be confirmed as part of a DBPCFC (double-blind placebo-controlled food challenge) during screening based on age-appropriate dose-limiting allergy symptoms at > 3 mg to ≤ 300 mg peanut protein. The severity grading of occurring reactions was performed according to the Practical Allergy (PRACTALL) guideline adapted for young children. Randomisation was carried out at a 2:1 ratio, stratified by region (North America vs Europe). During the entire study period, the children from both study arms had to follow a peanut-avoidant diet. The dosage regimen of the active ingredient peanut protein was divided into 3 phases: initial dose escalation (2 days), dose escalation (24 to 40 weeks) and maintenance (12 to 24 weeks). Children who developed moderate or severe symptoms in the initial dose escalation phase on day 1 or day 2 and children who did not tolerate the dose of 300 mg over 2 weeks within 40 weeks discontinued the study prematurely.
Dose adjustment was largely possible during dose escalation and maintenance in accordance with the product information. In the ARC005 study, a 12-month duration of the entire treatment phase (initial dose escalation, dose escalation and maintenance) was planned. After reaching the maximum duration of the maintenance phase, treatment with the study medication was terminated and the exit DBPCFC was performed. The primary endpoint in the ARC005 study was tolerance of 1,000 mg peanut protein in Europe and tolerance of 600 mg peanut protein in the exit DBPCFC with no more than mild symptoms in North America.
The study was conducted in several study sites in the USA and Europe (France, Germany, United Kingdom) between November 2018 and July 2022.

The appropriate comparator therapy "monitoring wait-and-see approach" was operationalised in the ARC005 study as adherence to a peanut-avoidant diet. For reasons of blinding, a placebo was administered in the control arm. If indicated, emergency medication could also be administered in both arms. The appropriate comparator therapy is therefore considered to be adequately implemented in the ARC005 study.

Extent and probability of the additional benefit

Mortality

Overall mortality

There were no deaths in the ARC005 study.

Morbidity

Allergic reactions due to accidental exposure to peanuts

In the ARC005 study, the children had to follow a peanut-avoidant diet throughout the study. In the event of accidental peanut exposure during the study, the guardians were instructed to contact the study site within 24 hours, regardless of whether an adverse reaction had occurred. Besides accidental exposure to peanut, exposure to other food allergens was also documented. A special case report form for exposure to food allergens was used to record accidental exposure and any reaction to it.

For the endpoint of allergic reactions due to accidental exposure to peanuts, there was no statistically significant difference between the treatment groups.

Absence of symptoms at all doses tested (maximum 2,000 mg) in the exit DBPCFC (double-blind, placebo-controlled food challenge) and

maximum symptom severity at all doses tested (maximum 2,000 mg) in the exit DBPCFC

DBPCFC is a double-blind, placebo-controlled provocation to food and involves two provocation tests: on one day, the food to be tested is used and on another, a placebo preparation is used. Food provocation using DBPCFC is considered the established standard in the present indication. In the ARC005 study, the patients in the DBPCFC received peanut flour on one day and a taste-masked, food-based placebo on another day in ascending doses at intervals of 20 to 30 minutes. The provocation tests were not allowed to be more than 7 days apart. In the ARC005 study, two DBPCFCs took place during the study, at the time of screening (screening DBPCFC) and at the end of the treatment phase (exit DBPCFC). In the DBPCFC, the child was tested for tolerance to consecutive single doses of peanut protein (or placebo). A maximum of 300 mg peanut protein (cumulative 444 mg) was provoked in the screening DBPCFC. In the exit DBPCFC, provocation was up to a maximum of 2,000 mg (cumulative 4,043 mg). During the DBPCFC, the children were medically monitored by a study doctor, who was neither involved in their treatment during the study nor in the assessment of AEs occurring during the study.
The collection and severity grading of occurring symptoms were carried out for the assessment of the tolerance of a particular dose in the DBPCFC in accordance with the Practical Allergy (PRACTALL) guideline. The PRACTALL classification system has been adapted to young children. A dose was considered tolerated if, after intake, either no symptoms occurred or the symptoms developed were mild, did not occur in more than 1 organ system, did not worsen, resolved on their own without therapeutic intervention within 1 hour and did not include objective wheezing. Children, in whom the dose escalation phase lasted 40 weeks and who did not tolerate the 300 mg dose for 2 weeks, were not allowed to participate in the exit DBPCFC.
The severity grading of the endpoints of maximum symptom severity and absence of symptoms at all doses tested (up to 2,000 mg) was carried out according to CoFAR (Consortium for Food Allergy), thus according to a classification system other than that for the assessment of the tolerance of a respective dose in the DBPCFC. The severity grades according to CoFAR range from 1 (mild) to 5 (death). Children who did not develop any symptoms were assigned grade 0. The endpoint of absence of symptoms at all doses tested (up to 2,000 mg) in the exit DBPCFC corresponds to the characteristic manifestation 0-no symptoms of the endpoint of maximum symptom severity at all doses tested (maximum 2,000 mg) in the exit DBPCFC. The evaluation was done post hoc. Missing values of the maximum symptom severity at all doses tested in the exit DBPCFC were replaced with the values from the screening

DBPCFC. In contrast to the provocation in the exit DBPCFC (up to a maximum of 2,000 mg), the provocation in the screening DBPCFC was only up to a maximum of 300 mg peanut protein.

The successful passing of a medically supervised food provocation is described in the literature as a surrogate for the efficacy of desensitisation. In everyday life, various co-factors can have an influence on the allergic reaction after accidental peanut exposure. For example, sporting activity or an acute illness can influence the extent of the allergic reaction. Furthermore, the "dose" of accidental peanut exposure is variable. These influencing factors are excluded or controlled within the framework of a DBPCFC. In the ARC005 study, for example, the children were only allowed to take part in the DBPCFC if they did not have an acute illness. In addition, antihistamines and other medications should be discontinued for a defined period of time prior to DBPCFC.

In the written statement procedure, the scientific-medical societies and clinical experts expressed the view that the quantities of peanut protein administered in a provocation were deliberately chosen to be so high that the transferability of clinically relevant desensitisation to everyday life is ensured. The target threshold value of 2,000 mg peanut protein, which was increased again in the present study, was significantly higher than the dose to be expected in everyday life in the event of accidental exposure, so that the influence caused by co-factors could be considered negligible.
However, no data were presented for the present benefit assessment that show with sufficient certainty that a significant increase in the threshold in the provocation test leads (in the long term) to a correspondingly significantly reduced risk of (severe) allergic reactions in everyday life. From the G-BA's point of view, it is therefore not possible - based on data from the DBPCFC - to predict with sufficient certainty the future risk or frequency of allergic reactions after peanut exposure, or the severity of future allergic reactions after peanut exposure in everyday life. The endpoints "Absence of symptoms at all doses tested (maximum 2,000 mg) in the exit DBPCFC" and "Maximum symptom severity at all doses tested (up to 2,000 mg) in the exit DBPCFC" evaluated post hoc by the pharmaceutical company are therefore not considered per se as a valid surrogate for the occurrence of allergic reactions after accidental peanut exposure in everyday life. However, the absence of symptoms during the provocation test and the reduction in symptom severity after taking a provocation dose are considered patient-relevant.

For the endpoint "Absence of symptoms at all doses tested (maximum 2000 mg) in the exit DBPCFC", there is a statistically significant advantage of peanut protein over the monitoring wait-and-see approach.

For the endpoint "Maximum symptom severity at all doses tested (maximum 2,000 mg) in the exit DBPCFC", there was no statistically significant difference between the treatment groups for the severity grade "severe" (grade ≥ 3).

Although an advantage of peanut protein over placebo is observed with regard to absence of symptoms in the exit DBPCFC, this is not reflected in the patient-relevant endpoint "Allergic reactions due to accidental exposure to peanuts", which is independent of the provocation test. It is unclear whether this is solely due to the short duration of the study. Whether the advantage in the provocation test is reflected in a reduction of allergic reactions (both reactions due to accidental exposure as well as in general) in the further course therefore remains unclear on the basis of the available data and can only be answered by a longer study duration and follow-up.

Quality of life

No data are available for the category of health-related quality of life.

Side effects

In the dossier, the pharmaceutical company presents post hoc evaluations of AEs with and without consideration of the events of the underlying disease. Only the evaluations of AEs that include events of the underlying disease are used for the benefit assessment.

Severe AEs, serious adverse events (SAEs)

For the endpoints of severe AEs and SAEs, there were no statistically significant differences between the treatment groups.

Therapy discontinuation due to AEs

For the endpoint of discontinuation due to AEs, no statistically significant difference was detected between the treatment groups.

Specific AEs

For the endpoint of systemic allergic reactions (AEs), there was no statistically significant difference between the treatment groups. Severe systemic allergic reactions (severe AEs) did not occur in the ARC005 study. For the endpoint of gastrointestinal disorders, there was a statistically significant difference to the disadvantage of AR101 compared to the monitoring wait-and-see approach.

Overall assessment

The results of the ARC005 study comparing peanut protein with placebo are available for the benefit assessment for children aged 1 to 3 years with a confirmed diagnosis of peanut allergy. The data allow comparative statements to be made versus the appropriate comparator therapy of the monitoring wait-and-see approach.

No events occurred in the mortality category during the study.

In the morbidity endpoint category, there was a statistically significant advantage of treatment with peanut protein over the monitoring wait-and-see approach for the "Absence of symptoms at all doses tested" endpoint assessed during the DBPCFC exit provocation test. There was no statistically significant difference in the patient-relevant endpoint "Allergic reactions due to accidental exposure to peanuts", which is independent of the provocation test, or in the endpoint "Maximum symptom severity at all doses tested".

No data are available for the category of health-related quality of life.

In the category of side effects, there were no relevant statistically significant advantages or disadvantages overall.

In the overall assessment, treatment with peanut protein shows an advantage in the endpoint on absence of symptoms as part of the provocation test under study conditions, which, however, could not be confirmed in patient-relevant endpoints outside of the provocation test. The extent to which the advantage in the provocation test is reflected in a reduction in allergic reactions due to accidental exposure and in general remains currently unclear. The extent of the advantage shown in the provocation test is therefore classified as non-quantifiable.

In summary, a non-quantifiable additional benefit compared with the appropriate comparator therapy of the monitoring wait-and-see approach is identified for children aged 1 to 3 years with a confirmed diagnosis of peanut allergy.

Reliability of data (probability of additional benefit)

The present benefit assessment is based on the results of the randomised, controlled and double-blind phase III ARC005 study. The risk of bias is estimated to be low at study level.

The risk of bias for the endpoint of discontinuation due to AEs and the endpoint of absence of symptoms at all doses tested (up to 2,000 mg) in the exit DBPCFC is assessed as low. For the endpoint of maximum symptom severity at all doses tested (maximum 2,000 mg) in the exit DBPCFC, the risk of bias is estimated to be high due to a large difference in the percentage of substituted values in the treatment arms.
For the other endpoints in the category of side effects, the discrepancy between the treatment arms in the percentage of children who discontinued the study prematurely (15.3% vs 6.3%) also resulted in a high risk of bias. In addition, follow-up was only carried out up to 14 days after the last dose of study medication.

Overall, the G-BA therefore derives a hint for the identified additional benefit with regard to the significance of the evidence.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts). The therapeutic indication assessed here is as follows: "Palforzia is indicated for the treatment of patients aged 1 to 3 years with a confirmed diagnosis of peanut allergy. Palforzia should be used in conjunction with a peanut-avoidant diet." The G-BA determined a monitoring wait-and-see approach as the appropriate comparator therapy.

The results of the ARC005 study comparing peanut protein with placebo are available for the benefit assessment for children aged 1 to 3 years with a confirmed diagnosis of peanut allergy. No events occurred in the mortality category during the study. In the morbidity endpoint category, there was a statistically significant advantage of treatment with peanut protein over the monitoring wait-and-see approach for the "Absence of symptoms at all doses tested" endpoint assessed during the DBPCFC exit provocation test. There was no statistically significant difference between the treatment groups in the patient-relevant endpoint "Allergic reactions due to accidental exposure to peanuts", which is independent of the provocation test, or in the endpoint "Maximum symptom severity at all doses tested". No data are available for the category of health-related quality of life. In the category of side effects, there were no relevant statistically significant advantages or disadvantages overall.

In the overall assessment, treatment with peanut protein shows an advantage in the endpoint on absence of symptoms as part of the provocation test under study conditions, which, however, could not be confirmed in patient-relevant endpoints outside of the provocation test. The extent to which the advantage in the provocation test is reflected in a reduction in allergic reactions due to accidental exposure and in general remains currently unclear. The extent of the advantage shown in the provocation test is therefore classified as non-quantifiable.

In the overall assessment, a hint for a non-quantifiable additional benefit of peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) compared to the monitoring wait-and-see approach was 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 information is based on the data provided by the pharmaceutical company in the dossier.

The calculation of the number of patients in the overall assessment is subject to uncertainty. The estimated percentage values for the prevalence of peanut allergy and for the percentage of patients without contraindications relate partly to different age groups. In addition, sources for the percentage values estimated by the pharmaceutical company are partly missing.

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 Palforzia (active ingredient: peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts)) freely available at the following link (last access: 17 April 2025):

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

Treatment with peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) should only be initiated and monitored by specialists experienced in the treatment of allergies.

The initial build-up dosing and the first dose of each new dose escalation level shall be administered under medical supervision in a specialised healthcare facility ready to treat potentially severe allergic reactions. The patient must have adrenaline (epinephrine) available for self-injection at all times.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material includes instructions on how to deal with the any side effects caused by peanut protein, especially anaphylaxis and eosinophilic oesophagitis.

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 June 2025).

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 for the maximum treatment duration, if specified in the product information.

Children aged 1 to 3 years with a confirmed diagnosis of peanut allergy

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts)	Continuously, 1 x daily	365.0	1	365.0
Appropriate comparator therapy				
monitoring wait-and-see approach	Not calculable			

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 co-morbidities) are not taken into account when calculating the annual treatment costs.

The build-up dosing and dose escalation phase for peanut protein as the medicinal product to be assessed covers a total period of 24 weeks. Due to this comparatively long period of time and the fact that the costs of the build-up dosing and dose escalation phase do not only result from a deviating dosage of the medicinal product, but also from additionally required SHI services, the initial build-up dosing and dose escalation phase is taken into account here in addition to the maintenance phase for presenting consumption. As a rule, no new titration or dose adjustment takes place after initial titration.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Peanut protein as defatted powder of Arachis hypogaega L., semen (peanuts)					
Initial build-up dosing	1 x 0.5 mg 1 x 1 mg 1 x 1.5 mg 1 x 3 mg	1 × 0.5 mg 1 x 1 mg 1 x 1.5 mg 1 x 3 mg	2 × 0.5 mg + 5 x 1 mg	1.0	2 × 0.5 mg + 5 x 1 mg
Dose escalation					
Phase 0	1 mg	1 mg	1 x 1 mg	14.0	14 x 1 mg
Phase 1	3 mg	3 mg	3 x 1 mg	14.0	42 x 1 mg
Phase 2	6 mg	6 mg	6 x 1 mg	14.0	84 x 1 mg
Phase 3	12 mg	12 mg	2 x 1 mg + 1 x 10 mg	14.0	28 x 1 mg + 14 x 10 mg
Phase 4	20 mg	20 mg	1 x 20 mg	14.0	14 x 20 mg
Phase 5	40 mg	40 mg	2 x 20 mg	14.0	28 x 20 mg
Phase 6	80 mg	80 mg	4 x 20 mg	14.0	56 x 20 mg
Phase 7	120 mg	120 mg	1 x 20 mg + 1 x 100 mg	14.0	14 x 20 mg + 14 x 100 mg
Phase 8	160 mg	160 mg	3 x 20 mg + 1 x 100 mg	14.0	42 x 1 mg + 14 x 100 mg
Phase 9	200 mg	200 mg	2 x 100 mg	14.0	28 x 100 mg
Phase 10	240 mg	240 mg	2 x 20 mg + 2 x 100 mg	14.0	28 x 20 mg + 28 x 100 mg
Phase 11	300 mg	300 mg	1 x 300 mg	14.0	14 x 300 mg
Maintenance phase	300 mg	300 mg	1 x 300 mg	196.0	196 x 300 mg
Maintenance phase,	300 mg	300 mg	1 x 300 mg	365.0	365 x 300 mg
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				

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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

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					
Peanut protein as defatted powder of *Arachis hypogaega L.*, semen (peanuts)[2]					
Peanut protein - initial build-up dosing 0.5 mg/ 1 mg	PO 13 W	€ 14.67	€ 1.77	€ 0.19	€ 12.71
Peanut protein - dose escalation - phase 1 - 3 mg	PO 48 W	€ 58.33	€ 1.77	€ 2.60	€ 53.96
Peanut protein - dose escalation - phase 2 - 6 mg	PO 96 W	€ 58.33	€ 1.77	€ 2.60	€ 53.96
Peanut protein - dose escalation - phase 3 - 12 mg	PO 48 W	€ 58.33	€ 1.77	€ 2.60	€ 53.96
Peanut protein - dose escalation - phase 4 - 20 mg	PO 16 W	€ 58.33	€ 1.77	€ 2.60	€ 53.96
Peanut protein - dose escalation - phase 5 - 50 mg	PO 32 W	€ 58.33	€ 1.77	€ 2.60	€ 53.96
Peanut protein - dose escalation - phase 6 - 80 mg	PO 64 W	€ 58.33	€ 1.77	€ 2.60	€ 53.96
Peanut protein - dose escalation - phase 7 - 120 mg	PO 32 W	€ 105.35	€ 1.77	€ 5.21	€ 98.37
Peanut protein - dose escalation - phase 8 - 160 mg	PO 64 W	€ 105.35	€ 1.77	€ 5.21	€ 98.37
Peanut protein - dose escalation - phase 9 - 200 mg	PO 32 W	€ 105.35	€ 1.77	€ 5.21	€ 98.37
Peanut protein - dose escalation - phase 10 - 240 mg	PO 64 W	€ 105.35	€ 1.77	€ 5.21	€ 98.37
Peanut protein - dose escalation - phase 11 - 300 mg[3]	PO 15 W	€ 105.35	€ 1.77	€ 5.21	€ 98.37
Appropriate comparator therapy					
Monitoring wait-and-see approach	Not calculable				
Abbreviations: POW = powder					

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[2] Peanut protein - dose escalation - phase 0 - 1 mg is not available in the LAUER-TAXE®. The calculation of the annual treatment costs is based on the package of the dose escalation phase 1, which contains the required potency of 1 mg peanut protein.

[3] The dose escalation phase 11 pack is the more economical option for presenting the maintenance phase with 300 mg peanut protein

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.

According to the product information, the patient must be prescribed adrenaline (epinephrine) for self-injection during treatment with Palforzia.
Notwithstanding this, peanut allergy sufferers are always advised to carry adrenaline (epinephrine) for self-injection due to the risk of anaphylaxis[4]. Consequently, the patient-individual costs for adrenaline (epinephrine) for self-injection due to the frequency of administration that varies from patient to patient can arise both with the use of the medicinal product to be assessed and under the appropriate comparator therapy.

The initial build-up dosing and the first dose of each new dose escalation level shall be administered under medical supervision in a specialised healthcare facility ready to treat potentially severe allergic reactions. These additionally required SHI services are incurred during treatment with the medicinal product to be assessed.

Designation of the therapy	Designation of the service		Costs per application	Number per year	Costs/ patient/ year
Medicinal product to be assessed					
Peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts)	Adrenaline injection product for self-injection 150 mg	Epinephrine 2 pre-filled pens	€ 105.42	Different from patient to patient	
	Oral hyposensitisation (desensitisation) treatment, follow-up ≥ 20 min as part of the build-up dosing phase (GOP 30133)		€ 7.68	4	€ 30.72
	Oral hyposensitisation (desensitisation) treatment, follow-up ≥ 60 min as part of the dose escalation phase (GOP 30134)		€ 19.33	12	€ 231.96
Appropriate comparator therapy					

[4] German guideline on acute therapy and management of analyhaxia, update 2021: https://www.awmf.org/uploads/tx_szleitlinien/061-025l_S2k_Akuttherapie-Management-Anaphylaxie_2021-10.pdf

Designation of the therapy	Designation of the service		Costs per application	Number per year	Costs/ patient/ year
Monitoring wait-and-see approach	Adrenaline injection product for self-injection 150 mg	Epinephrine 2 pre-filled pens	€ 105.42	Different from patient to patient	

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2.5 Designation of 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 the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA 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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid

valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing

authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Children aged 1 to 3 years with a confirmed diagnosis of peanut allergy

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) (Palforzia); PALFORZIA powder for oral use for removal from capsules or sachets; last revised: December 2024

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

At their session on 7 January 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 14 January 2025, the pharmaceutical company submitted a dossier for the benefit assessment of peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts) to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 15 January 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient peanut protein as defatted powder of *Arachis hypogaea L.*, semen (peanuts).

The dossier assessment by the IQWiG was submitted to the G-BA on 11 April 2025, and the written statement procedure was initiated with publication on the G-BA website on 15 April 2025. The deadline for submitting statements was 6 May 2025.

The oral hearing was held on 26 May 2025.

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 24 June 2025, and the proposed draft resolution was approved.

At their session on 3 July 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	7 January 2025	Determination of the appropriate comparator therapy
Working group Section 35a	14 May 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	26 May 2025	Conduct of the oral hearing
Working group Section 35a	4 June 2025 18 June 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	24 June 2025	Concluding discussion of the draft resolution
Plenum	3 July 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 3 July 2025

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

Prof. Hecken