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) (peanut allergy, ≥ 4 years of age)

of 7 April 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

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

According to Section 35a paragraph 3 SGB V, the G-BA 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 relevant date for the first placing on the (German) market of the active ingredient peanut protein as defatted powder of Arachis hypogaea L., semen (peanuts) in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 15 October 2021. 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 14 October 2021.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 17 January 2022, 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, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has 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 has 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) according to the product information

Palforzia is indicated for the treatment of patients aged 4 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 07.04.2022):

see therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy and patients who turn 18 during therapy

Appropriate comparator therapy for peanut protein as defatted powder of Arachis hypogaea L., semen (peanuts):

Watchful waitingCriteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication 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.

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

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.

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

on 1. In the therapeutic indication, there are no approved medicinal products for the treatment of peanut allergy as part of immunotherapy.

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

on 3. For the treatment of peanut allergy, there are no resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

There are a few methodologically high-quality review papers and guidelines for the treatment of food allergies. However, this literature does not refer specifically to the treatment of peanut allergy, but mainly to the (emergency) management of anaphylactic reactions as well as the long-term treatment of IgE-mediated food allergy. The recommendations focus on adherence to an allergen-eliminating diet on the one hand and on the provision and emergency use of adrenaline auto-injectors on the other. For the therapeutic indication of the treatment of peanut allergy as part of immunotherapy, no specific recommendations can currently be derived from the aggregated evidence, irrespective of a restriction regarding patient age.

In the absence of specific recommendations for the treatment of peanut allergy and against the background that no medicinal products or treatment options are approved in the therapeutic indication, a "Watchful waiting" approach is defined as the appropriate comparator therapy. With regard to the implementation of the appropriate comparator therapy, a peanut-avoiding diet is assumed in all study arms within the scope of a study. Furthermore, it is assumed that the use of emergency medication is possible in all study arms in case of accidental exposure and clinical necessity. This emergency medication is given as needed and is not a standard immunotherapy treatment for peanut allergy.

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

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:

Patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy and patients who turn 18 during therapy

For patients with a confirmed diagnosis of peanut allergy aged 4 to 17 years and patients who turn 18 years during therapy, the additional benefit of peanut protein as defatted powder of Arachis hypogaea L., semen (peanuts) compared to watchful waiting is not proven.

Justification:

The benefit assessment is based on the two double-blind RCTs PALISADE (ARC003) and ARTEMIS (ARC010). The ARC003 and ARC010 studies are both randomised, double-blind studies to investigate the safety and efficacy of immunotherapy with peanut protein as defatted powder of Arachis hypogaea L., semen (peanuts) (in short: peanut protein) versus placebo. Patients aged 4-55 years (ARC003) and 4-17 years (ARC010) were enrolled.

In addition to a defined serum concentration of IgE antibodies against peanut within the last 12 months and/or a defined mean wheal diameter after a peanut skin prick test compared to the negative control, the diagnosis of peanut allergy was confirmed in a double-blind placebo-controlled food challenge (DBPCFC) at screening. Inclusion criteria were dose-limiting symptoms at ≤ 100 mg peanut protein in the ARC003 study or at ≤ 300 mg in the ARC010 study. The classification of the severity of reactions occurred with minor deviations from the Practical Allergy (PRACTALL) guidelines.

In the ARC003 study, 555 patients were randomised in a 3:1 ratio to either peanut protein treatment (N = 416) or placebo (N = 139). The relevant sub-population of children and adolescents aged 4 to 17 years includes 374 children in the peanut protein arm and 125 children in the placebo arm. In the ARC010 study, 175 patients were randomised in a 3:1 ratio to either peanut protein treatment (N = 132) or placebo (N = 43). The median overall treatment duration was 331 and 328 days in the ARC003 study and 259 and 257 days in the ARC010 study in the intervention and control arms, respectively.

The dosing scheme of peanut protein is divided into an initial dose escalation of one day, a dose escalation phase (between 20 and a maximum of 40 weeks) in which the medication dose is built up daily at 2-week intervals starting at 3 mg up to a maintenance dose of 300 mg, and a maintenance phase with a daily dose of 300 mg (24 to 28 weeks in ARC003 and 12 to 16 weeks in ARC010). The dosage of peanut protein in both studies was according to the product information. During the entire study period, the patients had to follow a peanut-avoiding diet.

Allergic reactions were recorded at the study site according to established criteria and classified according to severity grade. For the treatment of acute allergic reactions, antihistamines and/or adrenaline could be given as emergency medication, and if indicated, also together with intravenous infusions, beta-adrenoceptor agonists, oxygen and/or steroids.

After reaching the maximum duration of the maintenance phase, treatment with the study medication was terminated and a DBPCFC (exit DBPCFC) was executed. Primary endpoint in

both studies was tolerating 1,000 mg of peanut protein (in the ARC003 study, only 600 mg of peanut protein in North America) with no more than mild symptoms at exit DBPCFC. In addition, in the course of the study, further patient-relevant endpoints on morbidity and side effects were collected.

The pharmaceutical company submitted two further studies (ARC004 and ARC007) with the dossier in addition to the two phase III RCTs ARC003 and ARC010. These studies are not considered for the benefit assessment. The ARC004 study, as an open-label extension study of the ARC003 study, does not allow for a comparison with the appropriate comparator therapy. In contrast, although the ARC007 study is a double-blind, North American-based, placebo-controlled RCT that included children aged 4 to 17 years with IgE-mediated peanut allergy, the enrolled patients were only in the maintenance phase for a fortnight after completing the build-up dosing. Furthermore, the median and mean treatment durations of less than 6 months in the ARC007 study are too short to allow conclusions about effects of immunotherapy with peanut protein in the context of the benefit assessment.

Overall, the evaluations of the two ARC003 and ARC010 studies are therefore used for the benefit assessment. The ARC003 and ARC010 studies are largely comparable with regard to the study design, the inclusion and exclusion criteria and the characteristics of the patients enrolled. Differences exist in the protocol-defined maximum tolerated dose of peanut protein at the time of enrolment in the study, the treatment duration and the site of implementation. However, the differences are not serious, so that the two ARC003 and ARC010 studies can be combined in meta-analytic terms.

Regardless of this, due to the high percentage of study dropouts and the resulting missing values for the endpoints collected in the exit DBPCFC, as well as any incomplete observations of the AE endpoints in some of the study participants, there is a high risk of bias in the results. Thus, 21.5% vs 8.1% (ARC003) and 19.7% vs 7.0% (ARC010) of the study participants discontinued the study prematurely, and the respective endpoints were not followed up until the end of the study. For this reason, a methodological adjustment of the variance was made for the AE endpoints in the meta-analysis, so that overall a high certainty of results is nevertheless assumed for these endpoints. There is still a high risk of bias in the endpoints collected in the exit DBPCFC. Especially in the case of effects in favour of the intervention, the risk of bias in the direction of an advantage for the intervention must be taken into account.

In addition, there are further limitations that can be traced back to the chosen study design as well as the data collection and evaluation. For example, only very limited data are available for patients with a confirmed diagnosis of peanut allergy who turn 18 during therapy. Also, on the basis of the available data, only statements on short-term effects of a peanut protein therapy are possible. Both of these factors limit the reliability of data of the assessment, because it cannot be ruled out that a treatment with peanut protein is a long-term therapy.

Extent and probability of the additional benefit

Mortality

Overall mortality

There were no deaths in the ARC003 and ARC010 studies.

Morbidity

Allergic reactions due to accidental exposure to peanuts

In the ARC003 and ARC010 studies, patients had to follow a peanut-avoidant diet throughout the study. In case of accidental peanut exposure during the study, patients were instructed to contact the study site to record any allergic reactions. Furthermore, it was documented in the electronic patient diary. If necessary, this was followed by a study visit. Besides accidental exposure to peanut, exposure to other food allergens was also documented. A special case report form for accidental 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 is no statistically significant difference between the treatment groups.

Absence of symptoms at all doses tested (maximum 1,000 mg) in the exit DBPCFC (double-blind, placebo-controlled food challenge)

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 ARC003 and ARC010 studies, the patients in the DBPCFC received peanut flour on one day and oat flour on another (placebo provocation) in ascending doses at intervals of 20 to 30 minutes. The provocation tests were not allowed to be more than 7 days apart. In both studies, 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 patient was tested for tolerance to consecutive single doses of peanut protein (or placebo). This involved provoking up to a maximum of 100 mg of peanut protein (cumulative 143 mg) in the screening DBPCFC in the ARC003 study and up to a maximum of 300 mg of peanut protein (cumulative 443 mg) in the ARC010 study. In the exit DBPCFC, provocation was up to a maximum of 1,000 mg (cumulative 2043 mg) in both studies. Patients were medically monitored during DBPCFC by a doctor who was not involved in the administration or escalation of the study medication and who did not assess AEs occurring in this context. The classification of the severity of reactions occurred with minor deviations from the PRACTALL guidelines. A dose was considered tolerated if after ingestion there were either no symptoms or the symptoms developed were mild or moderate and non-systemic, resolving on their own without any therapeutic intervention. Patients who did not reach the 300 mg dose by week 40 were not allowed to participate in the exit DBPCFC.

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. Therefore, based on the DBPCFC, it is not possible 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.

Therefore, the endpoint "absence of symptoms at all doses tested (maximum 1,000 mg) in the exit DBPCFC" defined post hoc by the pharmaceutical company is not considered per se a valid surrogate for the occurrence of allergic reactions after accidental peanut exposure in everyday life. The absence of symptoms during provocation testing is considered patient-relevant. For the endpoint "absence of symptoms at all doses tested (maximum 1,000 mg) in the exit DBPCFC", there is a statistically significant advantage of peanut protein over watchful waiting.

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 of 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 advantages in provocation testing are reflected in a reduction of allergic reactions (both reactions due to accidental exposure as well as in general) in the further course can only be answered by a longer study duration/follow-up.

Maximum symptom severity in all tested doses of peanut protein in the exit DBPCFC

The principal investigator graded the severity of any reactions that occurred, with minor deviations from the PRACTALL guidelines. The reduction in symptom severity after taking a provocation dose is patient-relevant. The uncertainties mentioned in the statements on DBPCFC for the endpoint "absence of symptoms at all doses tested (maximum 1,000 mg) in the exit DBPCFC" apply equally to this endpoint.

For the endpoint "maximum symptom severity at all tested doses of peanut protein in the exit DBPCFC", there is a statistically significant advantage of peanut protein over watchful waiting.

Quality of life

Food Allergy Independent Measure (FAIM), Food Allergy Quality of Life Questionnaire (FAQLQ)

The pharmaceutical company submits evaluations on the *Food Allergy Independent Measure* (FAIM) and *Food Allergy Quality of Life Questionnaire* (FAQLQ) instruments for the ARC003 and ARC010 studies and assigns them to health-related quality of life. The FAQLQ is an instrument for assessing morbidity/ health-related quality of life in patients with food allergies. The FAIM is an instrument to assess the patient's perceived risk of food allergy. For both instruments, evaluations of patient-reported versions (for the age groups 8 to 12 years and 13 to 17 years) as well as evaluations of surveys of parents (for the age groups 4 to 12 years and 13 to 17 years) were presented.

Notwithstanding the examination of the validity of the instruments, the assessment of the instruments FAQLQ and FAIM conducted in the studies is not suitable to adequately record patient-reported morbidity/ health-related quality of life in the present indication. For both measurement instruments, various methodological limitations arise against the background of the selected survey time points, the selected setting, the reference period and the evaluated percentage of <70% of the study participants. Overall, there are therefore no usable data on health-related quality of life.

However, these data would have been important to assess the influence of long-term peanut protein therapy with a peanut-avoiding diet on the patients.

Side effects

Serious adverse events (SAEs), severe AEs

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

Discontinuation due to AEs

For the endpoint of discontinuation due to AEs, there is a statistically significant difference to the disadvantage of peanut protein versus watchful waiting.

Specific AEs

For the endpoint of systemic allergic reactions, there is a statistically significant difference to the disadvantage of peanut protein versus the monitoring wait-and-see approach. For the endpoint of severe systemic allergic reactions, however, there is no statistically significant difference between the treatment groups.

For the endpoints of abdominal pain, abdominal pain in the upper body, itching in the oral cavity, oral paraesthesia, tightness in the throat (PT, AE in each case) and ear and labyrinth disorders (SOC, AE), a statistically significant difference to the disadvantage of peanut protein compared to watchful waiting was shown in each case.

The observed disadvantages of peanut protein - with the exception of discontinuations due to AEs - are not only evident in the initial dose escalation phase, but also occur in the maintenance phase. Particularly in the case of systemic allergic reactions, no decrease in the significantly increased risk compared to the control arm is recognisable in the course of the study.

<u>Overall assessment / conclusion</u>

For patients with a confirmed diagnosis of peanut allergy aged 4 to 17 years and for patients who turn 18 years during therapy, the results of the two ARC003 and ARC010 studies are

available for the benefit assessment of peanut protein. These studies allow comparative conclusions for peanut protein versus watchful waiting.

No events occurred in the mortality category during the study.

In summary, the endpoint category of morbidity for the endpoints collected during the DBPCFC exit provocation test on "absence of symptoms at all doses tested" and "maximum symptom severity at all doses of peanut protein tested" each show statistically significant advantages for treatment with peanut protein over the monitoring wait-and-see approach. In the patient-relevant endpoint "allergic reactions due to accidental exposure to peanuts", which is independent of the provocation test, there are no statistically significant advantages or disadvantages.

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

In the category of side effects, disadvantages can be derived for treatment with peanut protein compared to the appropriate comparator therapy of watchful waiting. Thus, for the endpoint "discontinuation due to AEs", there is a statistically significant disadvantage for peanut protein compared to the monitoring wait-and-see approach, while no advantages or disadvantages can be derived for the overall rate of SAEs and severe AEs respectively. The overall disadvantage for peanut protein seen in the side effects category is also reflected in detail in the specific AEs.

In the overall assessment, treatment with peanut protein shows advantages in the endpoints on symptomatology in the context of provocation testing under study conditions, which, however, could not be confirmed in patient-relevant endpoints outside of the provocation testing. In the morbidity endpoint of allergic reactions due to accidental exposure to peanuts, there is no statistically significant difference between the treatment groups. Statements on quality of life, which play a central role in the present therapeutic indication, are not possible due to the non-usable data. The endpoints on side effects show only negative effects. In terms of side effects, a significant disadvantage of treatment with peanut protein is found overall compared to watchful waiting.

In a weighing decision, the G-BA comes to the conclusion that in this case neither the disadvantages in terms of side effects nor the advantages, which are shown exclusively in morbidity endpoints in the context of the Food Challenge DBPCFC, predominate.

As a result, for patients with a confirmed diagnosis of peanut allergy aged 4 to 17 years and patients who turn 18 years during therapy, the additional benefit compared to the appropriate comparator therapy of watchful waiting is not proven.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of the new medicinal product Palforzia with the active ingredient peanut protein as defatted powder of Arachis hypogaea L., semen (peanuts). The therapeutic indication assessed here is as follows:

"for the treatment of patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. The use can be continued in patients aged 18 years and older. Use must be in conjunction with a peanut-free diet."

The G-BA determined watchful waiting as the appropriate comparator therapy.

For the benefit assessment of a treatment with peanut protein, the results of the two RCTs ARC003 and ARC010 are available, each of which investigates a treatment with peanut protein versus watchful waiting.

No events occurred in the mortality category during the study. In summary, for the endpoint of morbidity, treatment with peanut protein shows statistically significant advantages in symptomatology as part of the provocation test, but these advantages could not be confirmed in the endpoints outside of the provocation test. In the category of side effects, statistically significant disadvantages can be derived for peanut protein compared to watchful waiting, especially for the endpoints of discontinuation due to AEs and systemic allergic reactions, while no advantages or disadvantages are seen for the overall rate of SAEs or serious AEs. Overall, a significant disadvantage of treatment with peanut protein compared to watchful waiting is found in the side effects. Due to the chosen study design, the described methodological limitations and the resulting biases, uncertainties remain overall.

Overall, for patients with a confirmed diagnosis of peanut allergy aged 4 to 17 years and patients who turn 18 years during therapy, the additional benefit of peanut protein compared to watchful waiting is not proven.

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 size of the target population is subject to uncertainties in the overall assessment and may also be underestimated in the upper limit.
Uncertainties arise, among other things, due to the uncertain range of the percentage of patients with contraindications for a therapy with peanut protein. The prevalence data used by the pharmaceutical company is also based on a presumably wider range in the reality of care. In addition, due to the fact that it cannot be ruled out that treatment with peanut protein is a long-term therapy that will increasingly include patients up to adulthood in the future, it is assumed that the upper limit is underestimated.

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: 10 December 2021):

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 doctors experienced in the therapy of patients with peanut allergy.

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.

Peanut protein treatment is intended for children and adolescents aged 4 to 17 years and for adolescents who reach adulthood during treatment. Only very limited data are available for patients who reach adulthood during treatment.

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 March 2022).

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 is patient-individual 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.

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	1	365
Appropriate comparator therapy				

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
watchful waiting	incalculable			

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 build-up dosing and dose escalation phase for peanut protein as the medicinal product to be assessed here covers a total period of 22 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 usually exclusively considered 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 according to potency/ day of treatment	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Peanut protein as defatted powder of Arachis hypogaea 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 x 6 mg	1 × 0.5 mg 1 x 1 mg 1 x 1.5 mg 1 x 3 mg 1 x 6 mg	2 × 0.5 mg + 11 x 1 mg	1	2 × 0.5 mg + 11 x 1 mg
Dose escalation –					
Phase 1	3 mg	3 mg	3 x 1 mg	14	42 x 1 mg
Phase 2	6 mg	6 mg	6 x 1 mg	14	84 x 1 mg
Phase 3	12 mg	12 mg	2 x 1 mg + 1 x 10 mg	14	28 x 1 mg + 14 x 10 mg
Phase 4	20 mg	20 mg	1 x 20 mg	14	14 x 20 mg
Phase 5	40 mg	40 mg	2 x 20 mg	14	28 x 20 mg
Phase 6	80 mg	80 mg	4 x 20 mg	14	56 x 20 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption according to potency/ day of treatment	Treatment days/ patient/ year	Annual average consumption by potency
Phase 7	120 mg	120 mg	1 x 20 mg + 1 x 100 mg	14	14 x 20 mg + 14 x 100 mg
Phase 8	160 mg	160 mg	3 x 20 mg + 1 x 100 mg	14	42 x 1 mg + 14 x 100 mg
Phase 9	200 mg	200 mg	2 x 100 mg	14	28 x 100 mg
Phase 10	240 mg	240 mg	2 x 20 mg + 2 x 100 mg	14	28 x 20 mg + 28 x 100 mg
Phase 11	300 mg	300 mg	1 x 300 mg	14	14 x 300 mg
Maintenance phase	300 mg	300 mg	1 x 300 mg	210 -365	210 x 300 mg - 365 x 300 mg
Appropriate comparator therapy					
watchful waiting	Incalculable				

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. If a fixed reimbursement rate is available, this will be used as the basis for calculating the costs.

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
Peanut protein as defatted powder of Arachis hypogaega L., semen (peanuts)					
Peanut protein - initial build-up dosing 0.5 mg / 1 mg	13 POW	€ 26.87	€ 1.77	€ 0.94	€ 24.16
Peanut Protein - dose escalation - phase 1 1 mg	48 POW	€ 240.80	€ 1.77	€ 13.16	€ 225.87
Peanut Protein - dose escalation - phase 2 1 mg	96 POW	€ 240.80	€ 1.77	€ 13.16	€ 225.87
Peanut protein - dose escalation - phase 3 1 mg / 10 mg	48 POW	€ 240.80	€ 1.77	€ 13.16	€ 225.87
Peanut protein - dose escalation - phase 4, 20 mg	16 POW	€ 240.80	€ 1.77	€ 13.16	€ 225.87
Peanut protein - dose escalation - phase 5, 20 mg	32 POW	€ 240.80	€ 1.77	€ 13.16	€ 225.87
Peanut protein - dose escalation - phase 6, 20 mg	64 POW	€ 240.80	€ 1.77	€ 13.16	€ 225.87
Peanut protein - dose escalation - phase 7, 20 mg/ 100 mg	32 POW	€ 240.80	€ 1.77	€ 13.16	€ 225.87
Peanut protein - dose escalation - phase 8, 20 mg/ 100 mg	64 POW	€ 240.80	€ 1.77	€ 13.16	€ 225.87
Peanut protein - dose escalation - phase 9, 100 mg	32 POW	€ 240.80	€ 1.77	€ 13.16	€ 225.87
Peanut protein - dose escalation - phase 10, 20 mg/ 100 mg	64 POW	€ 240.80	€ 1.77	€ 13.16	€ 225.87
Peanut protein - dose escalation - phase 11, 100 mg and maintenance therapy 300 mg	15 POW	€ 240.81	€ 1.77	€ 13.16	€ 225.88
Appropriate comparator therapy					
watchful waiting	incalculable				
Abbreviations: POW = powder					

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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[2]. 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 cannot be quantified at present and, moreover, are incurred in the context of the build-up dosing and dose escalation phase in treatment with peanut protein with a frequency that varies from patient to patient.

Designation of the therapy	Designation of the service	Costs per application		Number per year
Medicinal product to be assessed				
Peanut protein as defatted powder of Arachis hypogaea L., semen (peanuts)	Adrenaline injection product for self-injection	Epinephrine 1 pre-filled pen	€ 66.64	Varies from patient to patient
	Medical monitoring in the context of the build-up dosing and dose escalation phase	Incalculable[3]		Varies from patient to patient
Appropriate comparator therapy				
watchful waiting	Adrenaline injection product for self-injection	Epinephrine 1 pre-filled pen	€ 66.64	Varies from patient to patient

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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.

[2] 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

[3] The additionally required SHI services cannot be quantified at this point in time.

4. Process sequence

At its session on 11 October 2016, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy determined by the G-BA was reviewed. At its session on 11 February 2020, the Subcommittee on Medicinal Products confirmed the appropriate comparator therapy.

On 14 October 2021, 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 14 October 2021 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 13 January 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 17 January 2022. The deadline for submitting written statements was 7 February 2022.

The oral hearing was held on 21 February 2022.

By letter dated 22 February 2022, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 11 March 2022.

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 29 March 2022, and the proposed resolution was approved.

At its session on 7 April 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	11 October 2016	Determination of the appropriate comparator therapy

Subcommittee Medicinal product	11 February 2020	Examination of the appropriate comparator therapy
Working group Section 35a	15 February 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	21 February 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	1 March 2022 15 March 2022 22 March 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	29 March 2022	Concluding discussion of the draft resolution
Plenum	7 April 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 7 April 2022

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

Prof. Hecken