Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 7 April 2022, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. The active ingredient peanut protein as defatted powder of Arachis hypogaea L., semen (peanuts) is added to Annex XII in alphabetical order as follows:

Benefit assessment procedure comprises several resolutions.
Please note the current version of the Pharmaceuticals Directive/Annex XII.

Courtesy translation – only the German version is legally binding.

Peanut protein as defatted powder of Arachis hypogaea L., semen (peanuts)

Resolution of: 7 April 2022
Entry into force on: 7 April 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

-Therapeutic indication (according to the marketing authorisation of 17 December 2020):

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 7 April 2022):

see therapeutic indication according to marketing authorisation

Benefit assessment procedure comprises several resolutions. Please note the current version of the Pharmaceuticals Directive/Annex XII.

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

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

Appropriate comparator therapy:

Watchful waiting

Extent and probability of the additional benefit of peanut protein as defatted powder of Arachis hypogaea L., semen (peanuts) versus monitoring wait-and-see approach:

An additional benefit is not proven.

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↑	Advantages in absence of symptoms and reduction of symptom severity during provocation testing.
Health-related quality of life	n.a.	There are no assessable data.

[1] Data from the dossier assessment of the IQWiG (A21-135) and from the addendum (A22-29), unless otherwise indicated.

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Side effects	↓↓	Disadvantages in discontinuations due to AEs, in systemic allergic reactions and in detail in specific AEs

Explanations:
↑: statistically significant and relevant positive effect with low/unclear reliability of data
↓: statistically significant and relevant negative effect with low/unclear reliability of data
↑↑: statistically significant and relevant positive effect with high reliability of data
↓↓: statistically significant and relevant negative effect with high reliability of data
↔: no statistically significant or relevant difference
∅: There are no usable data for the benefit assessment.
n.a.: not assessable

PALISADE study (ARC003; 4 to ≤ 55 years): Peanut protein vs placebo
Study design: randomised, double-blind, two-armed
Relevant sub-population: Children and adolescents aged 4 to ≤ 17 years

ARTEMIS study (ARC010; only children aged 4 years and older and adolescents aged ≤ 17 years): Peanut protein vs placebo
Study design: randomised, double-blind, two-armed

and a meta-analysis of both studies

Mortality

Endpoint **Study**	**Peanut protein**		**Placebo**		**Peanut protein vs Placebo**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Overall survival[b]					
ARC003	372	0 (0)	124	0 (0)	–
ARC010	132	0 (0)	43	0 (0)	–

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Morbidity

Endpoint **Study** **Study phase**	**Peanut protein**		**Placebo**		**Peanut protein vs Placebo**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]; Absolute difference (AD)[c]
Allergic reactions due to accidental exposure to peanuts					
ARC003					
Total treatment phase[d]	372	32 (8.6)[d]	124	13 (10.5)[e]	0.82 [0.45; 1.51]; 0.528
Maintenance phase	*310*[f]	*11 (3.5)*[g]	*118*[f]	*6 (5.1)*[g]	–
ARC010					
Total treatment phase[d]	132	3 (2.3)[d]	43	2 (4.7)[e]	0.49 [0.08; 2.83][h]; 0.481[i]
Maintenance phase	*108*[f]	*1 (0.9)*	*41*[f]	*0 (0)*	–
Total[j]					0.78 [0.44; 1.38]; 0.388

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Endpoint Study Study phase	Peanut protein		Placebo		Peanut protein vs Placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]; Absolute difference (AD)[c]
Absence of symptoms at all doses tested (maximum 1,000 mg) in the exit DBPCFC (double-blind, placebo-controlled food challenge)					
ARC003	372[k]	140 (37.6)	124[k]	3 (2.4)	15.56 [5.05; 47.94]; < 0.001 AD: 35.2%
ARC010	132[k]	47 (35.6[g])[l]	43[k]	0 (0)	31.43 [1.98; 499.27][h]; < 0.001[i, l] AD: 35.6%
Total[j]					17.83 [6.28; 50.58]; < 0.001
Maximum symptom severity at all doses of peanut protein in the exit DBPCFC					
ARC003					
mild	372	119 (32.0)	124	35 (28.2)	–
moderate	372	94 (25.3)	124	73 (58.9)	–
severe	372	19 (5.1)	124	13 (10.5)	0.49 [0.25; 0.96]; 0.045 AD: 5.4%
ARC010					
mild	132	55 (41.7)	43	16 (37.2)	–
moderate	132	24 (18.2)	43	20 (46.5)	–
severe	132	6 (4.6)	43	7 (16.3)	0.28 [0.10; 0.79]; 0.018 AD: 12.3%
Total[j]					0.41 [0.24; 0.73]; 0.002

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Health-related quality of life

Endpoint Study	Peanut protein		Placebo		Peanut protein vs Placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]
Food Allergy Independent Measure (FAIM); Food Allergy Quality of Life Questionnaire (FAQLQ)					
ARC003	No usable data available[m]				
ARC010	No usable data available[m]				

Side effects

Endpoint Study Study phase	Peanut protein		Placebo		Peanut protein vs Placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]; Absolute difference (AD)[c]
AEs (supplementary)					
ARC003					
Total treatment phase[d]	372	367 (98.7)	124	118 (95.2)	_
Maintenance phase	*310*[f]	*270 (87.1)*	*118*[f]	*94 (79.7)*	_
ARC010					
Total treatment phase[d]	132	130 (98.5)	43	42 (97.7)	_
Maintenance phase	*108*[f]	*95 (88.0)*	*41*[f]	*32 (78.0)*	_

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Endpoint **Study** **Study phase**	**Peanut protein**		**Placebo**		**Peanut protein vs Placebo**
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]; Absolute difference (AD)[c]
Serious adverse events (SAE)					
ARC003					
Total treatment phase[d]	372	8 (2.2)	124	1 (0.8)	2.67 [0.34; 21.11]; 0.462
Maintenance phase	*310[f]*	*4 (1.3)*	*118[f]*	*1 (0.8)*	–
ARC010					
Total treatment phase[d]	132	130 (98.5)	43	42 (97.7)	0.16 [0.02; 1.18]; 0.150
Maintenance phase	*108[f]*	*95 (88.0)*	*41[f]*	*32 (78.0)*	–
Total[j]					0.99 [0.27; 3.63]; 0.993

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Endpoint Study Study phase	Peanut protein		Placebo		Peanut protein vs Placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]; Absolute difference (AD)[c]
Severe AEs[n]					
ARC003					
Total treatment phase[d]	372	16 (4.3)	124	1 (0.8)	5.33 [0.71; 39.81]; 0.085
Maintenance phase	*310[f]*	*8 (2.6)*	*118[f]*	*0 (0)*	–
ARC010					
Total treatment phase[d]	132	1 (0.8)	43	0 (0)	0.99 [0.04; 23.92]; > 0.999
Maintenance phase	*108[f]*	*0 (0)*	*41[f]*	*0 (0)*	–
Total[j]					3.88 [0.74; 20.40]; 0.109
Discontinuation due to AEs					
ARC003					
Total treatment phase[d]	372	43 (11.6)	124	2 (1.6)	7.17 [1.76; 29.15]; < 0.001 AD: 10.0%
Maintenance phase	*310[f]*	*4 (1.3)*	*118[f]*	*0 (0)*	–
ARC010					
Total treatment phase[d]	132	12 (9.1)	43	1 (2.3)	3.91 [0.52; 29.20]; 0.191
Maintenance phase	*108[f]*	*0 (0)*	*41[f]*	*0 (0)*	–
Total[j]					6.08 [1.93; 19.16]; 0.002

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Endpoint Study Study phase	Peanut protein		Placebo		Peanut protein vs Placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]; Absolute difference (AD)[c]
Systemic allergic reactions[o]					
ARC003					
Total treatment phase[d]	372	53 (14.3)	124	4 (3.2)	4.42 [1.63; 11.96]; < 0.001 AD: 11.1%
Maintenance phase	*310[f]*	*27 (8.7[g])*	*118[f]*	*2 (1.7[g])*	–
ARC010					
Total treatment phase[d]	132	16 (12.1)	43	1 (2.3)	5.21 [0.71; 38.16]; 0.075
Maintenance phase	*108[f]*	*8 (7.4[g])*	*41[f]*	*1 (2.4[g])*	–
Total[j]					4.58 [1.88; 11.15]; < 0.001
Severe systemic allergic reactions[o, p]					
ARC003					
Total treatment phase[d]	372	1 (0.3)	124	0 (0)[q]	1.01 [0.04; 24.52][h]; 0.728[i]
Maintenance phase	*310[f]*	*1 (0.3)*	*118[f]*	*0 (0)*	–
ARC010					
Total treatment phase[d]	132	0 (0)	43	0 (0)	–
Total[j]					– [l]

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Endpoint Study Study phase	Peanut protein		Placebo		Peanut protein vs Placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]; Absolute difference (AD)[c]
Abdominal pain (PT, AE)					
ARC003					
Total treatment phase[d]	372	194 (52.2)	124	30 (24.2)	2.16 [1.56; 2.99][h]; < 0.001[i] AD: 26.0%
Maintenance phase	*310[f]*	*46 (14.8)*	*118[f]*	*7 (5.9)*	–
ARC010					
Total treatment phase[d]	132	88 (66.7)	43	19 (44.2)	1.51 [1.06; 2.16][h]; 0.009[i] AD: 22.5%
Maintenance phase	*108[f]*	*24 (22.2)*	*41[f]*	*4 (9.8)*	–
Total[j]					1.90 [1.49; 2.43]; < 0.001
Abdominal pain in the upper body (PT, AE)					
ARC003					
Total treatment phase[d]	372	152 (40.9)	124	26 (21.0)	1.95 [1.36; 2.80][h]; < 0.001[i] AD: 19.9%
Maintenance phase	*310[f]*	*41 (13.2)*	*118[f]*	*9 (7.6)*	–
ARC010					
Total treatment phase[d]	132	14 (10.6)	43	5 (11.6)	0.91 [0.35; 2.39][h]; 0.886[i]
Maintenance phase	*108[f]*	*4 (3.7)*	*41[f]*	*0 (0)*	–
Total[j]					1.78 [1.27; 2.49]; < 0.001

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Endpoint Study Study phase	Peanut protein		Placebo		Peanut protein vs Placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]; Absolute difference (AD)[c]
Itching in the oral cavity (PT, AE)					
ARC003					
Total treatment phase[d]	372	151 (40.6)	124	20 (16.1)	2.52 [1.65; 3.83][h]; < 0.001[i] AD: 24.5%
Maintenance phase	*310[f]*	*39 (12.6)*	*118[f]*	*5 (4.2)*	–
ARC010					
Total treatment phase[d]	132	28 (21.2)	43	1 (2.3)	9.12 [1.28; 65.06][h]; 0.007[i] AD: 18.9%
Maintenance phase	*108[f]*	*6 (5.6)*	*41[f]*	*0 (0)*	–
Total[j]					2.83 [1.87; 4.28]; < 0.001
Oral paraesthesia (PT, AE)					
ARC003					
Total treatment phase[d]	372	65 (17.5)	124	8 (6.5)	2.71 [1.34; 5.48][h]; 0.005[i] AD: 11.0%
Maintenance phase	*310[f]*	*23 (7.4)*	*118[f]*	*2 (1.7)*	–
ARC010					
Total treatment phase[d]	132	52 (39.4)	43	9 (20.9)	1.88 [1.01; 3.49][h]; 0.028[i] AD: 18.5%
Maintenance phase	*108[f]*	*18 (16.7)*	*41[f]*	*1 (2.4)*	–
Total[j]					2.27 [1.42; 3.63]; < 0.001

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Endpoint Study Study phase	Peanut protein		Placebo		Peanut protein vs Placebo
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI] p value[a]; Absolute difference (AD)[c]
Tightness in the throat (PT, AE)					
ARC003					
Total treatment phase[d]	372	86 (23.1)	124	8 (6.5)	3.58 [1.79; 7.18][h]; < 0.001[i] AD: 16.6%
Maintenance phase	*310*[f]	*20 (6.5)*	*118*[f]	*0 (0)*	–
ARC010					
Total treatment phase[d]	132	10 (7.6)	43	1 (2.3)	3.26 [0.43; 24.72][h]; 0.225[i]
Maintenance phase	*108*[f]	*1 (0.9)*	*41*[f]	*0 (0)*	–
Total[j]					3.55 [1.84; 6.85]; < 0.001
Ear and labyrinth disorders (SOC, AE)					
ARC003					
Total treatment phase[d]	372	48 (12.9)	124	3 (2.4)	5.33 [1.69; 16.82][h]; 0.001[i] AD: 10.5%
Maintenance phase	*310*[f]	*17 (5.5)*	*118*[f]	*0 (0)*	–
ARC010					
Total treatment phase[d]	132	21 (15.9)	43	5 (11.6)	1.37 [0.55; 3.41][h]; 0.582[i]
Maintenance phase	*108*[f]	*6 (5.6)*	*41*[f]	*1 (2.4)*	–
Total[j]					2.85 [1.40; 5.79]; 0.004

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a. Chi-square test.
b. Fatalities were recorded as part of AEs.
c. Indication of absolute difference (AD) only in case of statistically significant difference; own calculation.
d. Without events occurring in the exit DBPCFC.
e. The ARC003 study report shows that only a few of the events (maximum 8 vs 3 patients) were systemic allergic reactions. In contrast, the ARC010 study report shows that almost all (maximum 3 vs 1 patient) of the few events were systemic allergic reactions. The maximum data result from the fact that only the results for the predefined endpoint allergic reaction after accidental food exposure are reported in the study reports, independent of the food allergen. In both studies, neither severe systemic allergic reactions nor severe reactions after accidental food exposure occurred.
f. Number of patients who have reached the maintenance phase.
g. IQWiG's own calculation.
h. IQWiG's own calculation (asymptotic).
i. IQWiG's own calculation, CSZ test.
j. IQWiG's own calculation, fixed-effect model (Mantel and Haenszel method).
k. Missing measurement results in the exit DBPCFC (intervention vs comparator arm) were present in 76 (20.4%) vs 8 (6.5%) patients in the ARC003 study and 26 (19.7%) vs 3 (7.0%) patients in the ARC010 study. For these patients, it was assumed that no event occurred.
l. Conflicting data on the number of patients with an event in the intervention arm in module 4 A (47 or 52). The analysis with 52 patients with an event in the intervention arm results in an RR = 34.74. During the written statement procedure, the pharmaceutical company explained that 5 patients from the intervention arm had mild symptoms in the placebo provocation, but no symptoms in the peanut provocation (therefore rated as symptom-free).
m. Notwithstanding the assessment of the validity of the instruments, the assessment planned in the studies is not suitable to adequately record patient-reported morbidity/ health-related quality of life in the indication (see IQWiG benefit assessment).
n. Severe AEs ≥ grade 3: Severity classification for allergic reactions according to CoFAR, for systemic allergic reactions according to EAACI and for all other AEs according to CTCAE.
o. Defined according to Sampson diagnostic criteria (see IQWiG benefit assessment); coded as PT anaphylactic reaction.
p. Severity grade 3 (= severe) according to EAACI criteria.
q. 1 event occurred during exit DBPCFC when provoked with peanut.
r. Defined as the occurrence of maximum moderate symptoms in combination with predefined tolerance criteria (see IQWiG benefit assessment).
s. One or more adrenaline doses within a 2-hour window. It is assumed that the endpoint basically reflects both side effects and underlying disease/ disease-related morbidity, as events involving the use of adrenaline as an emergency medication for allergic reactions due to accidental exposure to peanuts (or other food allergens) are also included (see IQWiG benefit assessment).

Abbreviations used:
AD: Absolute difference; CoFAR: Consortium for Food Allergy Research; CTCAE: Common Terminology Criteria for Adverse Events; DBPCFC: Double-Blind Placebo-Controlled Food Challenge; EAACI: European Academy of Allergy and Clinical Immunology; FAIM: Food Allergy Independent Measure; FAQLQ: Food Allergy Quality of Life Questionnaire; CI: confidence interval; n: number of patients with (at least 1) event; N: number of patients evaluated; PT: Preferred Term; pU: pharmaceutical company; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; AE: adverse event; vs = versus

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2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 43,900 to 97,200 patients

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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.

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4. Treatment costs

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

Annual treatment costs:

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Peanut protein as defatted powder of Arachis hypogaea L., semen (peanuts)	First year: € 5,373.66
	Subsequent years: € 5,496.41
Additionally required SHI services	Different from patient to patient
Appropriate comparator therapy:	
Watchful waiting	Incalculable
Additionally required SHI services	Different from patient to patient

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II. The resolution will enter into force on the day of its publication on the website of the G-BA on 7 April 2022.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 7 April 2022

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

Prof. Hecken

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