Date: 8 June 2021
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

PALFORZIA

International non-proprietary name: allergens of peanut (*Arachis hypogaea*)

Pharmaceutical form: oral powder

Dosage strength(s):

- 1 mg, 20 mg, 100 mg, 300 mg
- 0.5 mg and 1 mg, 1 mg and 10 mg, 20 mg and 100 mg

Route(s) of administration: oral

Marketing Authorisation Holder: Medius AG

Marketing Authorisation No.: 67733

Decision and Decision date: approved on 4 May 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
AIT	Allergen immunotherapy
AllergO	Ordinance of the Swiss Agency for Therapeutic Products of 11 December 2009 on the Simplified Licensing of Allergen Preparations (Allergen Ordinance, SR 812.216.2)
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AR101	Peanut (*Arachis hypogaea*) allergens
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DBPCFC	Double-Blind, Placebo-Controlled Food Challenge
EoE	Eosinophilic oesophagitis
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
OLFC	Open-Label Food Challenge
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PPQ	Process performance qualification
PSP	Pediatric Study Plan (US-FDA)
Py	Patient years
RMP	Risk Management Plan
SIT	Specific immunotherapy
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPLRO	Ordinance of the Swiss Agency for Therapeutic Products of 9 November 2001 on the Licensing Requirements for Therapeutic Products (Therapeutic Products Licensing Requirements Ordinance, SR 812.212.22)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance allergens of peanut (*Arachis hypogaea*) of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Oral immunotherapy for patients with peanut allergy.

2.2.2 Approved Indication

PALFORZIA can be used to increase the peanut threshold dose tolerated without allergic reactions in patients aged 4 to 17 years with a confirmed* diagnosis of clinically significant peanut allergy.

* The following cumulative conditions must be met for a confirmed diagnosis:
- History of allergic reactions to peanut
- Confirmation of specific sensitisation (IgE and/or skin prick testing)
- Reaction in an oral challenge at a threshold dose of ≤ 300 mg peanut protein or confirmation of strong evidence of sensitisation (see RAMSES study in "Clinical efficacy" section).

PALFORZIA should only be used as an adjuvant measure in addition to a peanut-avoidant diet.

PALFORZIA may be continued in patients aged 18 years and older.

During the course of treatment, PALFORZIA raises the peanut threshold dose that can trigger a reaction. Fewer allergic reactions due to accidental exposure to peanut were seen with PALFORZIA compared with placebo during clinical development.

However, allergic reactions to PALFORZIA treatment (mostly to the preparation) were, overall, more frequent compared to placebo (mostly to food).

PALFORZIA is not intended for, and does not provide, immediate relief of allergic symptoms.
A sustained effect after stopping the treatment has not been shown.

2.2.3 Requested Dosage

Treatment with PALFORZIA is administered in 3 sequential phases: Initial Dose Escalation, Up-Dosing, and Maintenance. Initial Dose Escalation is conducted in a single day. Daily dosing of PALFORZIA is required during the Up-Dosing and Maintenance phases.
Initial Dose Escalation, the first dose of each new Up-Dosing level, and the first Maintenance dose are to be administered under the supervision of a health care professional qualified in the diagnosis and treatment of allergic diseases and in a health care setting prepared to manage potential severe allergic reactions.
Self-injectable adrenaline (epinephrine) must be prescribed to all patients.

Initial Dose Escalation
Initial Dose Escalation consists of 5 dose levels (0.5-6 mg; Table 1) administered over a duration of approximately 4-5 hours in a single day.
Patients who cannot tolerate doses up to, and including, the 3 mg single dose of PALFORZIA may not be suitable for treatment with PALFORZIA.

Up-Dosing
Initial Dose Escalation must be completed before starting Up-Dosing.

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During Up-Dosing, no more than 1 dose should be consumed per day. Patients must be instructed not to take a dose at home on the same day as a dose consumed in the clinic.
Patients are required to return to the health care setting approximately every 2 weeks for each subsequent assessment for a new Up-Dosing level.
Patients must complete all levels (Levels 1-11) of Up-Dosing prior to initiation of Maintenance dosing.
During Up-Dosing, subsequent doses of PALFORZIA are increased at 2-week intervals, if tolerated.
Patients should not progress through Up-Dosing more rapidly than the recommended 2-week intervals.
Up-Dosing requires administration of dose Levels 1-11 in sequential order: 3 mg, 6 mg, 12 mg, 20 mg, 40 mg, 80 mg, 120 mg, 160 mg, 200 mg, 240 mg, and 300 mg (corresponding to Levels 1-11, respectively) over a period of not less than 22 weeks.
If a patient cannot tolerate the first dose of the increased dose level, the patient should continue the previously tolerated dose level for a further 2 weeks or a dose reduction may be considered.

Maintenance Therapy
All dose levels of Up-Dosing (Levels 1-11) must be completed before starting with the ongoing therapeutic dose (Maintenance dose) of 300 mg per day.
No more than 1 dose should be consumed per day.
If a patient cannot tolerate the first Maintenance dose, the level should be reduced.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	14 October 2019
Formal control completed	7 November 2019
List of Questions (LoQ)	5 March 2020
Answers to LoQ	27 August 2020
Predecision	19 November 2020
Answers to Predecision	8 February 2021
Final Decision	4 May 2021
Decision	approval

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3 Medical Context

Peanut allergy can be directed against various peanut components. Its prevalence varies worldwide according to region, eating habits and cultural environment. Peanut allergies usually appear in early childhood, and although tolerance can develop spontaneously, this tends to be the exception. Treatment to date primarily involves the avoidance of triggering allergens. This can be difficult in severe forms of allergy. Since even small quantities of allergens can trigger reactions, accidental allergen exposures are possible even with a strict diet and good instruction/discipline, for example as a result of a contamination.

As for pollen and mite allergies, allergen immunotherapy with peanut allergens is also attempted for peanut allergies. Allergen immunotherapy (AIT, also known as specific immunotherapy, SIT) entails a controlled uptitration of specific allergens, to which the patients to be treated may respond with allergic reactions if the threshold dose is exceeded. As a result, the threshold dose may be increased and allergic reactions mitigated. As well as relieving allergic symptoms, allergology specialists postulate that AIT produces an improvement in the allergy that persists beyond the treatment period (known as desensitisation or hyposensitisation). The extent and mechanism of positive clinical effects of AIT have not yet been definitively clarified. To date, there are no long-term data that convincingly demonstrate a sustained effect, even after the discontinuation of treatment, that could not also be explained by selection bias as a result of increased study discontinuations during treatment compared to placebo. Allergen immunotherapy can be subdivided into various types based on the administration route. The most common routes are subcutaneous and sublingual administration. Oral administration into the gastrointestinal tract, as for Palforzia, is unusual. Unlike most sublingual immunotherapies, Palforzia contains predominantly digestion-resistant allergens.

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4 Quality Aspects

4.1 Drug Substance

AR101 peanut allergen source material is produced from raw shelled peanuts using a food-grade manufacturing process. The allergen source material is subject to its own specification, which is based on its requirements for use as a food ingredient.
The critical limits and in-process controls for manufacturing the source material have been established to ensure the taste/aroma profile, colour, and safety of the source material as a conventional food product.
The batch size for source material is determined by the amount of material produced from 2 or 3 lots of raw shelled peanuts. A portion of the batch produced is tested and released as AR101 drug substance, and this quantity of material is defined as the batch size of AR101 drug substance.
The AR101 drug substance process comprises selection of source material batches for AR101 drug substance, allergen source material receipt, drug substance release testing and lot disposition, and storage for drug product manufacturing.

AR101 drug substance has been characterised for content, protein profile, structural characteristics, immunological properties, biological activity, and physical characteristics. The characterisation results demonstrate that the AR101 drug substance allergen proteins were consistent over at least 7 different lots of AR101 drug substance that were used to manufacture clinical lots and commercial scale production (PPQ) batches.

The specifications include e.g. identity tests, purity and impurity and potency tests. All the analytical methods are described, and non-compendial methods have been validated in accordance with ICH guidelines.

Batch analysis results for drug substance lots used in phase 2 clinical studies, phase 3 clinical studies, and for PPQ activities are presented. Changes to analytical methods and the evolution of the drug substance release specification throughout development are described.

The drug substance is stored at 25°C. No significant changes were observed within the proposed storage conditions or under accelerated conditions. A shelf life of 36 months has been accepted.

4.2 Drug Product

AR101 drug product is supplied as an oral immunotherapy (OIT). AR101 drug product is presented in capsules of strengths 0.5, 1, 10, 20 and 100 mg and sachets of 300 mg. AR101 drug product is available in pull-apart hydroxypropyl methylcellulose (HPMC) capsules (0.5, 1, 10, 20 and 100 mg) and filled into sachets for maintenance dosing (300 mg). AR101 drug product oral powder is emptied from the capsule(s) or sachet before mixing with food. The capsules are not to be swallowed.

The manufacturing process of the finished drug product consists of blending, encapsulation, and sachet filling. Process validation studies have been completed for blending, encapsulation, and sachet filling.

The specifications for the drug product were set based on compendial requirements, and data from clinical trials and the commercial process. They include relevant tests and limits, e.g. for identity, quality, potency, and strength. All non-compendial methods are validated in accordance with ICH guidelines.

Batch analysis data are provided for the encapsulated AR101 drug product (0.5, 1, 10, 20, and 100 mg) and for AR101 drug product filled into sachets (300 mg). AR101 drug product manufactured during the development programme include phase 2 and phase 3 batches used in clinical studies and

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registration stability batches. Process performance qualification (PPQ) stability batches are also included and represent the commercial scale AR101 drug product (capsules and sachets).

The primary container closure system for the finished product consists of capsules (0.5 mg to 100 mg strengths) packaged into Aclar thermoformed blister strips with foil-backing. The thermoformed blister strip represents the primary container closure system for the encapsulated drug product.
Sachets with the 300 mg dosage strength are made from 2 sheets of a 3-layer foil-laminate film, which is heat sealed on 3 sides to form an open pouch. The fourth side is heat sealed after the sachet is filled. The sachet foil-laminate is composed of polyethylene terephthalate (PET)/aluminium foil/polyethylene (mPE).

The drug product is stored at no higher than 25°C. No significant changes were observed within the proposed storage conditions. A shelf life of 24 months has been accepted.

4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf lives of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies.

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5 Nonclinical Aspects

A nonclinical program to support the marketing authorisation application of Palforzia, oral powder (Peanut allergens from Arachis hypogaea) has not been carried out.

As the drug substance is derived from peanuts and peanut flour, i.e. commonly used foods and food additives eaten at levels appreciably higher than those proposed for clinical use, pharmacodynamic, pharmacokinetic, or toxicology studies have not been performed or considered warranted. Swissmedic accepted this in line with the European Medicines Agency (EMA). This approach complies with the legal framework for the authorisation of allergen products (Article 4 of the TPLRO and Article 12 of the AllergO).

The efficacy and safety of Palforzia are based solely on clinical studies.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

Palforzia is a protein powder obtained from peanuts by a standardised process and containing the clinically important peanut allergens (Ara h 1, Ara h 2, Ara h 6, Ara h 3, Ara h 7) and, to a lesser extent, other minor allergens. For administration, the powder is mixed with a soft food, such as yoghurt, and taken with a few spoonfuls of the latter. Depending on the dose, the powder is packed in a capsule (3 mg to 100 mg) or a sachet (300 mg). The treatment is administered in three consecutive phases:
Initial dose escalation: 0.5 mg to 6 mg in five increments under medical supervision.
Up-dosing: 3 mg to 300 mg in 11 increments; the first dose of each dose level is taken under supervision, after which the patients continue taking daily doses for two weeks/dose level themselves at home.
Maintenance: 300 mg/day; if treatment is interrupted for more than 3 days, the next dose must be taken under supervision, possibly with a dose reduction; if treatment is interrupted for more than 14 days, a further up-dosing process starting with 3 mg must be considered .

Pharmacokinetics: Allergens are polypeptides and proteins that are thought to be capable of being hydrolysed both in the gastrointestinal tract and (everywhere) in the tissues and broken down into small polypeptides. In accordance with pertinent guidelines, no specific pharmacokinetic studies were submitted.

Pharmacodynamics: The mechanism of action of specific immunotherapy has not been convincingly clarified to date. In this method of treatment, the 'pathogenic' allergens are administered with the aim of modifying the relevant immunity by stimulating specific B- and T-cell receptors.
Several studies with the proposed preparation have shown that the proposed administration leads to an increase in specific IgG4 antibodies against peanut allergens. During the first few months of treatment, there is also an increase in specific IgEs, which subsequently decline again. The studies also showed that the size of the wheals induced by skin prick testing with peanut allergen declined during the Palforzia treatment. An increase in the threshold dose to peanut allergens in patients with peanut allergy was also demonstrated clinically during the Palforzia treatment in the submitted studies. However, the persistence of this tolerance and the effects on the size of wheals induced by skin prick testing after discontinuation of treatment have not been investigated. As stated in the proposed dosage instruction, it must be assumed that the protective effect is lost if treatment is interrupted for longer than 14 days, hence the need to restart the full dose escalation process.

6.2 Dose Finding and Dose Recommendation

The recommended dosage for Palforzia is initially titrated over almost six months. Since the submitted data show that the start of treatment with the lowest dose is well tolerated by most patients it can be considered as sufficiently well documented from a safety perspective.
The dose-response relationship was not specifically investigated. The following summarised partial results of study ARC002 can be interpreted as indicating that an increase in the maintenance dose above 300 mg/day does not lead to better tolerance. However, scant data are available on this subject.

Study ARC001: In this double-blind, parallel-group study, placebo was compared with Palforzia in a total of 57 patients with peanut allergy. After an "initial dose escalation", up-dosing in 11 levels over at least 22 weeks and a maintenance treatment with 300 mg/day for 2 weeks, the proportion of patients who tolerated at least 300 mg of peanut protein (“responders”) was determined in a double-blind, placebo-controlled food challenge (DBPCFC). The proportion of patients who tolerated at least 300 mg in the DBPCFC after treatment, was statistically significantly higher, and numerically much higher, in the Palforzia group than in the placebo group. However, more treatment dropouts were described for Palforzia than the placebo group (6/29 versus 1/27).

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ARC002: In this open-label, follow-on study, Palforzia was administered, in gradually increasing doses, to the patients that had previously been treated with placebo in ARC001. Patients were then treated with the maintenance dose of 300 mg (recommended dosage regimen). If the 300 mg was well tolerated after 12-24 weeks at this dosage, an initial "Maintenance-DBPCFC" was implemented in the last 4 weeks. The proportion of “responders” among the patients previously treated with placebo was 20/26, compared to 20/21 (and 20/29 respectively) among those who had previously received Palforzia. In an "Extended Maintenance" phase, the dosage was further increased to 2000 mg/day. This was possible in 12/26 of those treated previously in ARC001 with placebo and in 14/21 and 14/29, respectively, in those treated previously in ARC001 with Palforzia; but this dose could be administered up until the end of the study only in 10 patients in each case. In the open-label food challenge (OLFC) following the Extended Maintenance phase, only three individuals were still taking part (all from the group of those treated previously in ARC001 with Palforzia). The maximum tolerated single dose in these three patients was 1000 mg.

6.3 Efficacy

The demonstration of efficacy is based on the two pivotal studies PALISADE and ARTEMIS and the "Real-World AR101 Market-Supporting Experience Study" RAMSES.

Study PALISADE is a double-blind, placebo-controlled 3:1 parallel-group comparison of Palforzia with "initial dose escalation", up-dosing in 11 levels over at least 22 weeks and a maintenance treatment with 300 mg/day for 25-28 weeks.
The study investigated patients aged from 4-55 years with peanut allergy, who were mainly defined by evidence of sensitisation (serologically or in the prick test) and a reaction in a double-blind placebo-controlled food challenge (DBPCFC) with peanut protein at a dose of ≤ 100 mg.
The primary endpoint was the proportion of patients aged 4-17 who tolerated a single dose of at least 600 mg (USA) or 1000 mg (Europe) in a DBPCFC following the treatment. "Key secondary" endpoints were DBPCFC responders at other challenge doses (300 mg, 1000 / 600 mg), the number of very severe reactions after the challenge and challenge results in patients aged 18-55.
More treatment dropouts occurred with the active treatment (Palforzia) (80/374 versus 10/125). The differences were attributed mainly to differing rates of AEs and patients who withdrew consent.
As regards the primary and key secondary endpoints in 4-17 year olds, significant differences were described between Palforzia and placebo.
In the relatively small subgroup of adults (18-55 years), the differences were just below the level of statistical significance.

Study ARTEMIS: Design intervention and endpoints were comparable with those of study PALISADE, except that the maintenance treatment was continued for only 12-16 weeks.
The investigated patients were aged 4-17 years, and the threshold dose in the randomisation DBPCFC had to be ≤ 300 mg, otherwise they were selected according to criteria comparable with those of study PALISADE.
Numerically, there were more treatment dropouts with Palforzia compared to placebo: 26/132 versus 3/40).
Efficacy: As regards the primary and key secondary endpoints in children and adolescents, significant differences were described between Palforzia and placebo.

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Endpoint	PALISADE		ARTEMIS	
	PALFORZIA N = 372	Placebo N = 124	PALFORZIA N = 132	Placebo N = 43
Primary Efficacy Endpoint				
Proportion of patients who tolerated 1000 mg peanut protein (95% CI) [1]	50.3% (45.2, 55.3)	2.4% (0.8, 6.9)	58.3% (49.4, 66.8)	2.3% (0.1, 12.3)
Treatment difference (PALFORZIA- placebo) [95% CI] [2]	47.8% (38.0, 57.7)		56.0% (44.1, 65.2	
P-value [2]	< 0.0001		< 0.0001	
Key Secondary Efficacy Endpoints				
Proportion of patients who tolerated 600 mg peanut protein (95% CI) [1]	67.2% (62.3, 71.8)	4.0% (1.7, 9.1)	68.2% (59.5, 76.0)	9.3% (2.6, 22.1)
Treatment difference (PALFORZIA- placebo) [95% CI] [2]	63.2% (53.0, 73.3)		58.9% (44.2, 69.3)	
Response rate: proportion of patients who tolerated 300 mg peanut protein (95% CI) [1]	76.6% (72.1, 80.6)	8.1% (4.4, 14.2)	73.5% (65.1, 80.8)	16.3% (6.8, 30.7)
Treatment difference (PALFORZIA- placebo) [95% CI] [2]	68.5% (58.6, 78.5)		57.2% (41.2, 69.3)	
P-value [2]	< 0.0001		< 0.0001	

Patients without an exit DBPCFC were counted as non-responders.

[1] PALISADE: Based on Wilson (score) confidence limits, ARTEMIS: Based on exact Clopper-Pearson interval.

[2] PALISADE: Based on the Farrington-Manning confidence limits. ARTEMIS: Based on exact unconditional confidence limits using the score statistic; p-values were based on Fisher's exact test.

Source: Information for healthcare professionals, Table 6

Study RAMSES was a double-blind, placebo-controlled 2:1 parallel-group comparison of a treatment with up-dosing until the dose of 300 mg/day was reached (dosage regimen as proposed). The whole study lasted a maximum of 48 weeks.
The patients were children aged 4-17 years with a history of peanut allergy and distinct sensitisation (serologically sensitised to peanut (≥14 kUA/L, in the skin prick test with wheals ≥ 8 mm)).
The primary goal was to investigate safety, including the frequency of anaphylactic reactions (defined as systemic allergic reaction) and adrenaline use.
More treatment dropouts occurred with Palforzia (78/338 versus 10/158). The differences were attributed mainly to differing rates of AEs and patients who withdrew consent.
Overall, more AEs, and a tendency towards more serious AEs, were described for the active treatment arm compared to placebo. The AEs occurred mainly during the initial dose escalation and the up-dosing phase.
More AEs, and particularly more anaphylactic reactions, were observed in the active arm compared to placebo, although there were fewer AEs involving accidental allergen exposure with no connection with the study medication.

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6.4 Safety

The documentation submitted on the clinical development to date included safety data for a total of about 1,000 patients and corresponding to a cumulative experience of around 1,000 patient years (py).
In the three controlled phase III studies, a total of 841 patients were exposed to Palforzia and 335 received placebo. The overall exposure in these controlled trials corresponds to around 350 patient years.
A total of 12 patients turned 18 years of age during the study treatment; eight were treated with Palforzia, four with placebo. Patients ≥ 18 years of age were investigated in a controlled study only in PALISADE, and the corresponding experience was equivalent to about 25 patient years.

Comparison with placebo (Controlled Population)
AEs, particularly systemic allergic reactions, were observed more frequently, overall, in the Palforzia than in the placebo arm. The AEs were usually mild or moderate and exhibited the pattern expected for this type of treatment. They mainly involved the gastrointestinal tract (oral/pharyngeal symptoms, abdominal pain, nausea/vomiting, rarely diarrhoea), the skin (pruritus, urticaria) and the conjunctivae/airways (rhino-conjunctivitis, cough). Events were more frequent during the initial dose escalation and up-dosing phases than during the maintenance phase with 300 mg/d. In the treatment arm, a connection with the study medication was assumed in 88.6% of the reactions, compared to 56.7% in the placebo arm. Systemic allergic reactions of all severities were observed more frequently in the Palforzia arm. In patients receiving Palforzia, the study medication was the most common presumed trigger (in 115/136 events), where food was usually the presumed trigger with placebo (in 12/15 events). The reactions were usually not life-threatening, and epinephrine was used in 5.7% of patients receiving the active treatment and 2.7% of the patients taking placebo. Severe systemic reactions were described in 10 patients. All 10 cases occurred during the treatment with Palforzia. Reactions were described both during the up-dosing phase and the maintenance phase. 8/10 reactions occurred within two hours after treatment (median: 54 minutes). The subgroup of presumed allergic events triggered by food was proportionally lower with the active treatment compared to placebo (171/841 vs 117/335). These differences were described both for the up-dosing phase and the maintenance phase. Peanut was the triggering food in less than half of the cases. Triggers other than peanut were proportionally more common with the active treatment versus placebo, in the dose escalation phase, whereas almost no differences are described between active treatment and placebo in the maintenance phase.

Frequencies including uncontrolled data
As regards frequencies and patterns, no new signals were found compared to the placebo-controlled studies, apart from the signal described below concerning eosinophilic oesophagitis (EoE). During the maintenance treatment, a trend towards a reduction in the frequency of AEs was described, but this may also have been partly attributable to the omission of patients with poor tolerability. As regards systemic allergic reactions, the increasing duration of treatment was not associated with a convincing reduction in the frequency of anaphylaxis that could not also be explained by drop-outs. In particular, the frequency of food-induced cases of anaphylaxis did not show any consistent reduction.
In the phase III studies, five EoE cases were described during the active treatment with Palforzia in around 900 py (versus 0 for placebo with around 100 py), three during the controlled study phase and two additional cases during the extension phases. The possibility that long-term treatment with Palforzia may promote the development of EoE is not ruled out by the submitted data.

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6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

The data submitted for the recommended treatment with Palforzia in children aged 4-17 years with severe peanut allergy show an increase in the peanut threshold dose to 1000 mg (corresponding to about 3 peanuts) in over half of the patients, whereas over 90% of the children treated with placebo were unable to tolerate doses above 100 mg. Allergic reactions thought to be triggered by food were proportionally less frequent during the active treatment with Palforzia versus placebo (171 events in 841 patients versus 117/335). The difference was even more pronounced for peanut-triggered events (47/841 versus 39/335). However, if treatment is interrupted for more than 14 days, an up-dosing process lasting several months, starting with 3 mg, must be implemented on resumption of treatment, regardless of the preceding duration of treatment.
The described benefit of what is presumably only a transient increase in the threshold dose is opposed by Palforzia-treatment-associated events. Overall, AEs were described more frequently for Palforzia (88.6% versus 56.7%). In particular, systemic allergic incidents were more common compared to placebo (112/841 versus 14/335). The reactions associated with Palforzia are not described as being more harmless than the peanut-associated reactions with placebo. Although the submitted documentation does indicate a reduction in the frequency of allergic reactions due to accidental peanut exposure, it also suggests that the partial and transient tolerance induction to peanut allergy is obtained at the expense of treatment-induced allergic reactions, and that the treatment with Palforzia leads to more anaphylactic reactions overall compared to placebo.
1/12 of the severe systemic reactions, which were presumably induced by Palforzia, occurred as late as 4 hours after treatment, and no co-factors for this reaction were identified. Consequently, the risk of such reactions is difficult to calculate, but possibly easier to assess than the risk of reactions induced by accidental peanut exposure.
Swissmedic considers that authorisation for appropriate use in patients aged 4-17 years is acceptable in specific situations. However, the information for healthcare professionals describes that the demonstrated effect of an increase in the threshold dose is limited to the duration of treatment, and that the incidence of allergic incidents observed overall for Palforzia is higher compared to placebo.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Palforzia was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See the section on "Adverse effects" for how to report adverse reactions.

PALFORZIA, oral powder

Composition

Active Ingredient

Allergens of peanut (*Arachis hypogaea*)

Excipients

PALFORZIA 0,5 mg, 1 mg, 10 mg, 20 mg:
Microcrystalline cellulose, partially pre-gelatinised maize starch, colloidal anhydrous silica, magnesium stearate.
PALFORZIA 100 mg und 300 mg:
Microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate.

Pharmaceutical Form and Amount of Active Ingredient per Unit

Oral powder.
PALFORZIA 0,5 mg
Each 0.5 mg capsule contains allergens of peanut (*Arachis hypogaea*) corresponding to 0.5 mg peanut protein.
PALFORZIA 1 mg
Each 1 mg capsule contains allergens of peanut (*Arachis hypogaea*) corresponding to 1 mg peanut protein.
PALFORZIA 10 mg
Each 10 mg capsule contains allergens of peanut (*Arachis hypogaea*) corresponding to 10 mg peanut protein.
PALFORZIA 20 mg
Each 20 mg capsule contains allergens of peanut (*Arachis hypogaea*) corresponding to 20 mg peanut protein.
PALFORZIA 100 mg
Each 100 mg capsule contains allergens of peanut (*Arachis hypogaea*) corresponding to 100 mg peanut protein.
PALFORZIA 300 mg
Each 300 mg sachet contains allergens of peanut (*Arachis hypogaea*) corresponding to 300 mg peanut protein.

Indication/Possible Applications

PALFORZIA can be used to increase the peanut threshold dose tolerated without allergic reactions in patients aged 4 to 17 years with confirmed* diagnosis of clinically significant peanut allergy.

* The following cumulative conditions must be met for a confirmed diagnosis:

- History of allergic reactions to peanut
- Confirmation of specific sensitisation (IgE and/or skin prick testing)
- Reaction in an oral challenge at a threshold dose of ≤ 300mg peanut protein or confirmation of strong evidence of sensitisation (see RAMSES study in section “Clinical efficacy”).

PALFORZIA should only be used as an adjuvant measure in addition to a peanut-avoidant diet.
PALFORZIA may be continued in patients aged 18 years of age and older.

During the course of treatment, PALFORZIA raises the peanut threshold dose that can trigger a reaction. Fewer allergic reactions due to accidental exposure to peanut were seen with PALFORZIA compared with placebo during clinical development.
However, allergic reactions to PALFORZIA treatment (mostly to the preparation) were overall more frequent than to placebo (mostly to food).

PALFORZIA is not intended for, and does not provide, immediate relief of allergic symptoms.
A sustained effect after stopping the treatment has not been shown.

Posology and method of administration

Initial Dose Escalation and the first dose of each new Up-Dosing level are to be administered under the supervision of a health care professional qualified in the diagnosis and treatment of allergic diseases and in a health care setting prepared to manage potential severe allergic reactions.

Treatment with PALFORZIA is administered in 3 sequential phases: Initial Dose Escalation, Up-Dosing, and Maintenance. Initial Dose Escalation is conducted in a single day. Daily dosing of PALFORZIA is required during the Up-Dosing and Maintenance phases.

Self-injectable adrenaline (epinephrine) must be prescribed to all patients.

Initial Dose Escalation

Initial Dose Escalation consists of 5 dose levels (0.5-6 mg; **Table 1**) administered over a duration of approximately 4-5 hours in a single day.

Patients should not have active wheezing, a flare of atopic disease (e.g. atopic dermatitis) or suspected intercurrent illness prior to initiation of therapy.

Patients should receive sequential dose escalation of PALFORZIA beginning at 0.5 mg. Each dose should be separated by an observation period of at least 20 to 30 minutes. Following completion of the last dose administered, the patient should be observed for at least 60 minutes or until suitable for discharge, in the opinion of the treating physician.

Table 1: Dose and Capsule Presentation for Initial Dose Escalation

Dose	Capsule Presentation per Dose
0.5 mg	1 × 0.5 mg capsule
1 mg	1 × 1 mg capsule
1.5 mg	1 × 0.5 mg capsule; 1 × 1 mg capsule
3 mg	3 × 1 mg capsules
6 mg	6 × 1 mg capsules

A dose can be considered tolerated if no more than transient mild symptoms are observed with no medical intervention/therapy required.

The administration of PALFORZIA must be discontinued if severe symptoms occur, especially if administration of adrenaline is required, with any dose during initial dose escalation (IDE). IDE dosing can be re-initiated in these patients at the discretion of the treating physician.

Patients who tolerate at least the 3 mg single dose of PALFORZIA during Initial Dose Escalation should return to the health care setting, preferably the next day, for initiation of Up-Dosing.

Patients who cannot tolerate doses up to and including the 3 mg single dose of PALFORZIA may not be suitable for treatment with PALFORZIA.

If a patient is unable to initiate Up-Dosing within 4 days of the Initial Dose Escalation, the Initial Dose Escalation should be repeated in a health care setting.

Up-dosing

Initial Dose Escalation must be completed before starting Up-Dosing.
Patients should not have active wheezing, a flare of atopic disease (e.g. atopic dermatitis) or suspected intercurrent illness prior to the administration of each new Up-Dosing level.

During Up-Dosing, no more than 1 dose should be consumed per day. Patients must be instructed not to take a dose at home on the same day as a dose is given in clinic.
Dose configurations for Up-Dosing are shown in **Table 2.**
Up-Dosing is initiated at a 3 mg dose (Level 1).

Patients are required to return to the health care setting approximately every 2 weeks for each subsequent assessment for a new Up-Dosing level.
Patients must complete all levels (Levels 1-11) of Up-Dosing prior to initiation of Maintenance dosing.

Table 2: Daily Dosing Configuration for Up-Dosing

Dose Level	Daily Dose	Presentation of Dose (Blister / Sachet)
1	3 mg	3 × 1 mg capsules
2	6 mg	6 × 1 mg capsules
3	12 mg	2 × 1 mg capsules; 1 × 10 mg capsule
4	20 mg	1 × 20 mg capsule
5	40 mg	2 × 20 mg capsules
6	80 mg	4 × 20 mg capsules
7	120 mg	1 × 20 mg capsule; 1 × 100 mg capsule
8	160 mg	3 × 20 mg capsules; 1 × 100 mg capsule
9	200 mg	2 × 100 mg capsules
10	240 mg	2 × 20 mg capsules; 2 × 100 mg capsules
11	300 mg	1 × 300 mg sachet

During Up-Dosing, subsequent doses of PALFORZIA are increased at 2-week intervals, if tolerated, as shown in **Table 2**. Patients should not progress through Up-Dosing more rapidly than the recommended 2-week intervals.

Up-Dosing requires administration of dose Levels 1-11 in sequential order: 3 mg, 6 mg, 12 mg, 20 mg, 40 mg, 80 mg, 120 mg, 160 mg, 200 mg, 240 mg, and 300 mg (corresponding to Levels 1-11, respectively) over a period of not less than 22 weeks.

The first dose of each Up-Dosing Level (Levels 1-11) of PALFORZIA is prepared and administered during a scheduled clinic visit. Patients should be observed for at least 60 minutes or until suitable for discharge, in the opinion of the treating physician.

A dose level can be considered tolerated if no more than transient mild symptoms are observed with no medical intervention/therapy required.

If the patient tolerates the first dose of the increased dose level, the patient may continue that daily dose level at home for a minimum of 2 weeks.

If a patient cannot tolerate the first dose of the increased dose level, the patient should continue the previously tolerated dose level for a further 2 weeks or a dose reduction may be considered (see “Dose Modification Guidelines”).

Maintenance Therapy

All dose levels of Up-Dosing (Levels 1-11) must be completed before starting with the ongoing therapeutic dose (Maintenance dose) of 300 mg per day.

No more than 1 dose should be consumed per day. Patients must be instructed not to take a dose at home on the same day as a dose is given in clinic.

The Maintenance dose is administered as a single 300 mg sachet.

The Maintenance dose can be considered tolerated if no more than transient mild symptoms are observed with no or minimal medical intervention/therapy required.

If a patient cannot tolerate the first Maintenance dose, the level should be reduced (see “Dose Modification Guidelines”).

Daily Maintenance is required to maintain the effect of Palforzia.
Efficacy data currently are available for up to 24 months of treatment with PALFORZIA.

Dose adjustment due to adverse effects/interactions

Dose Modification Guidelines
Dose modifications are not appropriate during Initial Dose Escalation.
Temporary dose modification of PALFORZIA may be required for patients who experience allergy symptoms during Up-Dosing or Maintenance.

Patients may be more likely to experience allergy symptoms following PALFORZIA dosing in the presence of a medical event such as an intercurrent illness (e.g. viral infection), exacerbation of asthma, or in the presence of other co-factors (e.g. exercise, menstruation, stress, fatigue, sleep deprivation or intake of nonsteroidal anti-inflammatory drugs or alcohol). Temporarily withholding or decreasing PALFORZIA doses may be required in the presence of these medical events or co-

factors.

Symptoms that last longer than 90 minutes and/or are severe, recurrent or bothersome should be clinically evaluated by the treating physician, and the best course of action should be determined, which can consist of maintaining the dose level for longer than 2 weeks, reducing or withholding PALFORZIA doses.
Prophylactic treatment of intercurrent symptoms may also be considered prior to dosing PALFORZIA and may include H1- and/or H2-antihistamines or a proton pump inhibitor.
Eosinophilic oesophagitis should be taken into consideration in patients with symptoms of oesophagitis (see section “Warnings and precautions”).

An Up-Dosing dose level can be maintained for longer than 2 weeks if a patient is unable to progress to the next level because of allergy symptoms or for practical reasons for patient management.

After a dose reduction, Up-Dosing to the Maintenance dose of PALFORZIA should be performed according to **Table 2**. If the patient tolerates the first dose of the increased dose level, the patient may continue that daily dose level at home for a minimum of 2 weeks.

Management of Consecutive Missed Doses

Missed doses of PALFORZIA may pose a significant risk to patients due to potential loss of treatment effects. The guidelines in **Table 3** are to be used at the discretion of the treating physician.

Table 3: Management of Consecutive Missed Doses

Consecutive Missed Doses	**Action**
1 to 2 days	Patients may resume PALFORZIA at the same dose level at home.
3 to 4 days	Patients may resume PALFORZIA at the same dose level under medical supervision in a health care setting based on medical judgment.
5 to 14 days	Patients may resume Up-Dosing with PALFORZIA under medical supervision in a health care setting at a dose of 50% or less of the last tolerated dose.
Greater than 14 days	Evaluate patient compliance and consider re-starting Up-Dosing at 3 mg under supervision in a health care setting.

Following a dose reduction due to missed doses, resume Up-Dosing as described in **Table 2**.

Advise patients that if a daily dose is missed, the next dose should be resumed at the usual time the following day.

If 3 or more consecutive doses are missed, patients should be advised to contact their health care provider. The next dose must be taken under medical supervision in a health care setting based on medical judgment. Consider the cause of missed doses and assess whether treatment should be altered or continued.

Elderly population

The safety and efficacy of PALFORZIA in adults > 55 years has not yet been established.

Paediatric population aged less than 4 years

The safety and efficacy of PALFORZIA in children aged < 4 years has not yet been established.

Method of administration

Capsules are not to be ingested and must be discarded when empty.
PALFORZIA oral powder must be taken orally after mixing with an age-appropriate soft food.
After emptying, the contents of each individual capsule or sachet should be mixed with soft food, such as yoghurt, apple sauce, pudding, or other palatable, age-appropriate food. The food must not be heated (no warmer than room temperature) and must be a food to which the patient is not additionally allergic. The volume of the vehicle food should be such that the entire dose of PALFORZIA can be consumed in a few spoonsful (see section “Other Instructions - Handling Instructions”).

Timing of doses
During Up-Dosing and Maintenance, when dosing at home it is recommended that each dose of PALFORZIA should be taken at a consistent time each day as part of a meal, preferably in the evening.

If the patient has been engaged in strenuous exercise prior to dosing, dosing should be delayed until signs of a hypermetabolic state (e.g. flushing, sweating, rapid breathing, and/or rapid heart rate) have passed.

Patients should avoid exercising, taking hot showers or baths prior to or within approximately 2 to 3 hours after dosing. Patients should not take PALFORZIA within 2 hours of bedtime.

Contraindications

PALFORZIA is contraindicated in patients with the following:

- Severe or uncontrolled asthma
- A history of eosinophilic oesophagitis (EoE); other eosinophilic gastrointestinal disease; chronic, recurrent, or severe gastroesophageal reflux disease (GERD); symptoms of dysphagia; or recurrent gastrointestinal symptoms of undiagnosed aetiology
- A history of severe mast cell disorder
- Hypersensitivity to any of the excipients as listed in the composition
- Uncontrolled arterial hypertension or cardiovascular diseases

Special warnings and precautions for use

Adrenalin

Self-injectable adrenaline must be prescribed to patients receiving PALFORZIA. Patients and caregivers must be instructed to recognise the signs and symptoms of an allergic reaction and in the proper use of self-injectable adrenaline. Instruct patients to seek immediate medical care upon its use and to stop treatment with PALFORZIA until they have been evaluated by a physician.

PALFORZIA may not be suitable for patients who are taking medications that can inhibit the effect of adrenaline:

- *Beta-adrenergic blockers*: Patients taking beta-adrenergic blockers may be unresponsive to the usual doses of adrenaline used to treat serious systemic reactions, including anaphylaxis. Specifically, beta-adrenergic blockers antagonise the cardio-stimulating and bronchodilating effects of adrenaline.
- *Alpha-adrenergic blockers, ergot alkaloids*: Patients taking alpha-adrenergic blockers may be unresponsive to the doses of adrenaline used to treat serious systemic reactions, including anaphylaxis. Specifically, alpha-adrenergic blockers antagonise the vasoconstricting and hypertensive effects of adrenaline. Similarly, ergot alkaloids may reverse the pressor effects of adrenaline.

PALFORZIA should be used with caution when taken in conjunction with medications that can potentiate the effect of adrenaline. These medications include the following:

- *Tricyclic antidepressants, monoamine oxidase inhibitors, and certain antihistamines*: The adverse effects of adrenaline may be potentiated in patients taking tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, and the antihistamines chlorpheniramine and diphenhydramine.
- *Cardiac glycosides, diuretics*: Patients who receive adrenaline while taking cardiac

glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

Systemic allergic reactions including anaphylaxis
When treated with PALFORZIA, peanut-allergic patients are exposed to peanut allergens that cause allergic symptoms. Therefore, allergic reactions to PALFORZIA are expected in these patients. These reactions are usually mild or moderate; however, more severe reactions may occur up to 4 hours after taking PALFORZIA. Dose modifications should be considered for patients who experience moderate or severe adverse allergic reactions to PALFORZIA (see “Dose Modification Guidelines”).

PALFORZIA can cause systemic allergic reactions including anaphylaxis, which may be life-threatening.
Do not initiate PALFORZIA treatment in a patient who has had severe or life-threatening anaphylaxis within the previous 60 days.

Severe adverse reactions such as difficulty swallowing, difficulty breathing, changes in voice or feeling of fullness in the throat require immediate treatment, including use of adrenaline, and subsequent medical evaluation.

Patients must be educated to recognise the signs and symptoms of allergic reactions. Patients should be instructed to contact a health care professional before administering the next dose of PALFORZIA if symptoms of an escalating or persistent allergic reaction occur. Patients should be instructed to promptly treat the reaction and seek immediate medical attention if they develop symptoms of a severe allergic reaction. Allergic reactions may require treatment with adrenaline.

Increase of the peanut threshold dose
PALFORZIA cannot achieve increase of the peanut threshold dose in all patients. Daily use of the 300 mg maintenance dose is required to maintain the increase once achieved.

Asthma
Ensure patients with asthma have their asthma under control prior to initiation of PALFORZIA. PALFORZIA has not been studied in patients on long-term systemic corticosteroid therapy.

Immunotherapy with PALFORZIA should be temporarily withheld if the patient is experiencing an acute asthma exacerbation. Re-evaluate patients who have recurrent asthma exacerbations and consider discontinuation of PALFORZIA.

Concomitant illnesses

PALFORZIA may not be suitable for patients with certain medical conditions that may reduce the ability to survive a severe allergic reaction or increase the risk of adverse reactions after adrenaline administration. Examples of these medical conditions include, but are not limited to, markedly compromised lung function (chronic or acute, e.g. severe cystic fibrosis), unstable angina, recent myocardial infarction, significant arrhythmias, cyanotic congenital heart disease, uncontrolled hypertension, and inherited metabolic disorders.

Eosinophilic oesophagitis (EoE)

EoE has been reported in association with OIT including PALFORZIA. Discontinue PALFORZIA and consider a diagnosis of EoE in patients who experience severe or persistent gastrointestinal symptoms, including dysphagia, gastroesophageal reflux, chest pain or abdominal pain.

Gastrointestinal adverse reactions

For chronic/recurrent gastrointestinal symptoms, especially upper gastrointestinal symptoms (nausea, vomiting, dysphagia), the potential for a diagnosis of EoE should be considered.

If patients develop chronic or recurrent gastrointestinal symptoms, dose modification may be considered.

Concomitant allergen immunotherapy

PALFORZIA has not been studied in subjects receiving concomitant allergen immunotherapy.

Interactions

No formal interaction studies have been performed with PALFORZIA.

Pregnancy and lactation

Pregnancy

Treatment with PALFORZIA should not be initiated during pregnancy. There are no data on the clinical experience of PALFORZIA in pregnant women.

Treatment with PALFORZIA is associated with a risk of allergic reactions including anaphylaxis, especially during the first 12-months of therapy. Anaphylaxis can cause a dangerous decrease in blood pressure, which could result in compromised placental perfusion and significant risk to a foetus during pregnancy. In addition, the effect of PALFORZIA on the immune system of the mother and foetus during pregnancy is unknown.

In patients who become pregnant under PALFORZIA, the benefits of continuing treatment with continued increased threshold dose should be weighed against the risks of PALFORZIA-induced anaphylactic reactions if treatment is continued.

Lactation

Data are not available to assess the effects of PALFORZIA on the breastfed child or on milk production and excretion in the nursing woman. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for PALFORZIA and any other potential adverse effects on the breastfed child from PALFORZIA or from the underlying maternal condition.

Fertility

There are no specific clinical or nonclinical data on the effects of PALFORZIA on fertility.

Effects on ability to drive and use machines

The effect on the ability to drive or use machines has not been specifically studied.

Undesirable effects

The safety profile of PALFORZIA in patients with peanut allergy aged 4-17 years is derived from 5 clinical studies involving 944 unique subjects who received at least 1 dose of PALFORZIA.

The most common treatment-related adverse events with PALFORZIA were abdominal pain, throat irritation, nausea, pruritus, vomiting, urticaria, oral pruritus, upper abdominal pain, and abdominal discomfort. Most adverse events were mild or moderate in severity.

The incidence of treatment-related adverse events was higher during Up-Dosing (85.7%) than Initial Dose Escalation (45.1%) and Maintenance (57.7%).

During the period of 0 to 13 weeks until the period of >52 weeks (during maintenance therapy with 300 mg/day), the incidence of adverse reactions usually decreased which may, in part, be due to study discontinuation in a small number of patients with severe adverse reactions and the resulting selection of the study population.

Of subjects who discontinued PALFORZIA (11.4%) did so due to 1 or more adverse events.
The majority of subjects discontinued during up dosing (8.7%) followed by initial dose escalation (2.1%) and all 300 mg/day dosing (1.2%). The most common adverse events leading to

discontinuation of study product during up dosing were abdominal pain, vomiting, nausea, and systemic allergic reaction, including anaphylaxis.

The median time from administration of PALFORZIA at study sites to onset of the first symptom ranged from 4 to 8 minutes. The median time from onset of the first symptom to resolution of the last symptom ranged from 15 to 30 minutes.

Tabulated list of treatment-related adverse events

Table 4 is based on data from the PALFORZIA clinical trial program. Listed events are divided into groups according to the MedDRA convention frequencies: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), and very rare (< 1/10,000).

Table 4. Treatment-Related Adverse Events

System Organ Class	Frequency	Treatment-related Adverse Event
Infections and infestations	*Common*	Conjunctivitis
Immune system disorders	*Very common*	Anaphylactic reaction (mild or moderate)
	Common	Anaphylactic reaction (severe)
Nervous system disorders	*Common*	Headache
	Uncommon	Dysgeusia Drooling
Eye disorders	*Common*	Eye pruritus Ocular hyperaemia Eye swelling
Ear and labyrinth disorders	*Common*	Ear pruritus
	Uncommon	Ear pain
Vascular disorders	*Common*	Flushing
Respiratory, thoracic, and mediastinal disorders	*Very common*	Throat irritation Cough Sneezing Throat tightness
	Common	Wheezing Dyspnoea Pharyngeal paraesthesia Chronic throat clearing Dysphonia
	Uncommon	Pharyngeal oedema Choking

Gastrointestinal disorders	*Very common*	Abdominal pain Nausea Vomiting Oral pruritus Abdominal discomfort Abdominal pain upper Paraesthesia oral Lip pruritus
	Common	Lip swelling Diarrhoea Dysphagia Gastro-oesophageal reflux disease
	Uncommon	Eosinophilic oesophagitis Swollen tongue Enlarged uvula
Skin and subcutaneous tissue disorders	*Very common*	Pruritus Urticaria Erythema Rash
	Common	Swelling face Angioedema
General disorders and administration site conditions	*Common*	Chest discomfort Chest pain Fatigue Sensation of foreign body
	Uncommon	Face oedema

Description of selected adverse reactions

Anaphylaxis (severe systemic allergic reactions)

For the purpose of reporting the clinical study results, the term systemic allergic reaction is used to describe anaphylactic reaction events of any severity and the term anaphylaxis is used to distinguish anaphylactic reaction events that were severe.

In controlled clinical trials systemic allergic reactions of any severity were observed more frequently with PALFORZIA than with placebo (136 events in 841 patients versus 15/335). By contrast, allergic reactions due to accidental exposure to peanut were less frequent with PALFORZIA than with placebo (47 events in 841 patients versus 39/335). The reactions were usually non-serious and the majority were mild to moderate. Adrenaline was used in 5.7% of patients taking Palforzia and in 2.7% of patients taking placebo. Ten patients experienced severe systemic reactions. All of these episodes occurred during treatment with Palforzia. In 8/10 cases the reactions occurred within 2 hours after treatment (median 54 minutes).

Eosinophilic oesophagitis (EoE)
EoE was diagnosed in 5 of 944 subjects (0.5%) in clinical trials and was considered treatment related in 3 of the subjects (0.3%). The severity of EoE was considered mild in 2 subjects (0.2%), moderate in 2 subjects (0.2%) and severe in 1 subject (0.1%). All 5 subjects with EoE were discontinued from study treatment.

Safety in patients aged 18 and over
The safety profile of PALFORZIA in patients who became 18 years old whilst participating in the phase 3 clinical trial program was similar to the safety profile of the overall 4 to 17 year-old population.

The reporting of suspected adverse reactions after authorisation is of great importance. It enables continuous monitoring of the risk-benefit balance of the medicinal product. Health professionals are encouraged to report any suspicion of a new or serious adverse reaction via the Online-Portal ElViS (Electronic Vigilance System). Information on this can be found at www.swissmedic.ch.

Overdose

Administration of PALFORZIA at greater than recommended doses in peanut allergic patients increases the risk of side effects, including the risk of systemic allergic reactions or severe single-organ allergic reactions. In the case of severe reactions such as angioedema, difficulty in swallowing, difficulty in breathing, changes in voice or a feeling of fullness in the throat, treat immediately with relevant symptomatic medicine(s) and follow-up with a medical evaluation.

Properties/effects

ATC-Code

V01AA08.

Mechanism of action

PALFORZIA can increase the peanut threshold dose tolerated without an allergic reaction in patients with peanut allergy.
The precise mechanism of the treatment is not fully understood.

Pharmacodynamic

An increase in peanut-specific IgG G4 was observed during treatment with Palforzia. This laboratory parameter change has not yet been shown to be of clinical relevance.

Based on current evidence, it must be assumed that the therapy-induced increase of the peanut

threshold dose will be lost within a few days after interruption or discontinuation of treatment. Daily maintenance dosing is required until evidence of disease modifying effects has been shown.

Clinical efficacy

In all PALFORZIA clinical studies, efficacy was measured using a DBPCFC. This food challenge is a model for real world accidental exposure to food allergens and was performed according to the Practical Allergy (PRACTALL) guidelines for safety, assessment, and scoring with modification to include a 600 mg protein dose (between the 300 mg and 1000 mg challenge doses).

Phase 2

ARC001, the first in-human study was a multicentre, randomised double-blind, placebo-controlled phase 2 study conducted for up to 9 months to demonstrate the efficacy of PALFORZIA compared with placebo in peanut-allergic subjects aged 4 to 26 years. At entry, subjects had dose limiting symptoms after consuming ≤ 100 mg of peanut protein in a DBPCFC. At the exit DBPCFC, 23 of 29 (79%) PALFORZIA-treated subjects versus 5 of 26 (19%) placebo-treated subjects tolerated the single highest dose of at least 300 mg peanut protein with no more than mild allergy symptoms after a median 22 weeks of treatment, including 2 weeks at 300 mg/day.

Phase 3

The efficacy of PALFORZIA was demonstrated in 2 randomised, double-blind, placebo-controlled, multicentre, phase 3 pivotal studies PALISADE and ARTEMIS. Both studies recruited patients with a documented history of peanut allergy, and dose limiting symptoms after consuming increasing doses of peanut protein at a screening DBPCFC. Subjects with a severe or life-threatening anaphylaxis event within 60 days and those with severe or uncontrolled asthma were excluded from the studies. Following blinded treatment over approximately 6 months of Up-Dosing and 3 or 6 months of Maintenance dosing with PALFORZIA, or placebo, subjects completed an exit DBPCFC to assess therapy-induced increase in the threshold dose tolerated without the occurrence of severe allergic reactions to peanut.

For the primary efficacy analysis population, PALISADE recruited 496 patients aged 4 to 17 years who received at least 1 dose of the study medication.

In this study, eligible subjects had dose limiting symptoms after consuming ≤ 100 mg of peanut protein at the screening DBPCFC. Demographic and baseline characteristics were well matched between treatment groups. Of the subjects treated with PALFORZIA in the primary analysis population, 72% had a medical history of systemic allergic reactions, 66% reported multiple food allergies, 63% had a medical history of atopic dermatitis, and 53% had a present or previous

diagnosis of asthma. The subject population for the primary analysis was 78% were white and 57% male. The median age of subjects was 9 years. After approximately 1 year of blinded study treatment (~ 6 months of Up-Dosing and ~ 6 months of Maintenance treatment), subjects completed an exit DBPCFC to assess increase in the threshold dose to peanut.

ARTEMIS recruited subjects aged 4 to 17 years of age in Europe. The primary efficacy analysis population consisted of 175 subjects aged 4 to 17 years who received at least 1 dose of study treatment. In this study, eligible subjects had dose-limiting symptoms after consuming ≤ 300 mg of peanut protein at the screening DBPCFC. Demographic and baseline characteristics were generally well matched between treatment groups. Of the subjects in the primary analysis group subjects had a medical history of food allergies other than peanut (61.4% AR101, 48.8% placebo), atopic dermatitis (59.1%, 51.2%), allergic rhinitis (47.7%, 37.2%), and asthma (42.4%, 32.6%). The median age was 8.0 years. More than half were male (54.3%) and most subjects were white (81.7%). After approximately 9 months of blinded study treatment (~ 6 months of Up-Dosing and ~ 3 months of Maintenance treatment), subjects completed an exit DBPCFC to assess increase of the threshold dose to peanut.

RAMSES (Real-World AR101 Market-Supporting Experience Study)
The study was a double-blind, placebo-controlled 2:1 parallel-group comparison of a treatment with up-dosing until the dose of 300 mg/day was reached. The whole study lasted a maximum of 48 weeks. The patients were in total 506 children and adolescents with a history of peanut allergy and distinct sensitization (serologically sensitized to peanut ≥14 kUA/L, skin prick test with wheals ≥ 8 mm). The primary goal was to investigate safety. More treatment dropouts and allergic events occurred with PALFORZIA (AR101) compared to placebo. However, on treatment with PALFORZIA there were fewer adverse events involving accidental allergen exposure with no connection with the study medication.

Efficacy data
The primary efficacy endpoint in both PALISADE and ARTEMIS was the proportion of subjects aged 4 to 17 years who tolerated a single highest dose of at least 1000 mg peanut protein with no more than mild symptoms at the exit DBPCFC. Key secondary endpoints in this age group included determination of the patient response rates after single doses of 300 mg and 600 mg peanut protein and the maximum severity of symptoms at the exit DBPCFC.

<u>Increase of the tolerated peanut threshold dose</u>
Overall, treatment with PALFORZIA in both PALISADE and ARTEMIS resulted in statistically significant differences compared to placebo regarding the proportion of subjects who tolerated a

single dose of 300, 600, or 1000 mg peanut protein with no more than mild allergy symptoms at the exit DBPCFC. The summary of the proportion for primary and secondary efficacy endpoints for the intention to treat (ITT) populations in both PALISADE and ARTEMIS are provided in **Table 6**.

Table 6: PALISADE and ARTEMIS: Summary of Response Rates for Primary and Secondary Efficacy Endpoints (ITT Population, 4-17 Years)

Endpoint	PALISADE		ARTEMIS	
	PALFORZIA N = 372	Placebo N = 124	PALFORZIA N = 132	Placebo N = 43
Primary Efficacy Endpoint				
proportion of subjects who tolerated 1000 mg peanut protein (95% CI) [1]	50.3% (45.2, 55.3)	2.4% (0.8, 6.9)	58.3% (49.4, 66.8)	2.3% (0.1, 12.3)
Treatment difference (PALFORZIA-placebo) [95% CI] [2]	47.8% (38.0, 57.7)		56.0% (44.1, 65.2)	
P-value [2]	< 0.0001		< 0.0001	
Key Secondary Efficacy Endpoints				
proportion of subjects who tolerated 600 mg peanut protein (95% CI) [1]	67.2% (62.3, 71.8)	4.0% (1.7, 9.1)	68.2% (59.5, 76.0)	9.3% (2.6, 22.1)
Treatment difference (PALFORZIA-placebo) [95% CI] [2]	63.2% (53.0, 73.3)		58.9% (44.2, 69.3)	
P-value [2]	< 0.0001		< 0.0001	
Response rate: proportion of subjects who tolerated 300 mg peanut protein (95% CI) [1]	76.6% (72.1, 80.6)	8.1% (4.4, 14.2)	73.5% (65.1, 80.8)	16.3% (6.8, 30.7)
Treatment difference (PALFORZIA-placebo) [95% CI] [2]	68.5% (58.6, 78.5)		57.2% (41.2, 69.3)	
P-value [2]	< 0.0001		< 0.0001	

Subjects without an exit DBPCFC were counted as non-responders.

[1] PALISADE: Based on Wilson (score) confidence limits, ARTEMIS: Based on exact Clopper-Pearson interval.

[2] PALISADE Based on the Farrington-Manning confidence limits. ARTEMIS: Based on exact unconditional confidence limits using the score statistic; p-values were based on Fisher's exact test.

In the completer population in PALISADE (all subjects that complete treatment and have an evaluable exit DBPCFC) PALFORZIA-treated subjects had response rates of 63.2%, 84.5%, and 96.3% for the

1000, 600, and 300 mg single dose challenge doses of peanut protein, respectively.

In the completer population in the ARTEMIS study, PALFORZIA-treated subjects had response rates of 72.6%, 84.9%, and 91.5% for the 1000, 600, and 300 mg single dose challenge doses of peanut protein, respectively.

Maximum severity of symptoms

These data (summarised in **Table 7**) show that at any dose of peanut protein tested, PALFORZIA-treated subjects developed fewer severe symptoms compared with placebo-treated subjects.

Table 7: PALISADE and ARTEMIS: Maximum Severity of Symptoms at Exit DBPCFC (ITT Population, 4-17 Years)

Endpoint	PALISADE		ARTEMIS	
	PALFORZIA N = 372	Placebo N = 124	PALFORZIA N = 132	Placebo N = 43
Maximum severity of symptoms at any challenge dose [1]				
None	140 (37.6%)	3 (2.4%)	47 (35.6%)	0 (0.0%)
Mild	119 (32.0%)	35 (28.2%)	55 (41.7%)	16 (37.2%)
Moderate	94 (25.3%)	73 (58.9%)	24 (18.2%)	20 (46.5%)
Severe	19 (5.1%)	13 (10.5%)	6 (4.5%)	7 (16.3%)
P-value [2]	< 0.0001		< 0.0001	

[1] Subjects without an exit DBPCFC were assigned the maximum severity of symptoms during the screening DBPCFC (no change from screening).

[2] Treatment difference was tested using the Cochran-Mantel-Haenszel statistic (with equally spaced scores) stratified by geographic region [Europe, North America (PALISADE) and Country (ARTEMIS)].

Response rates in subjects who turned 18 years during therapy

The response rate of PALFORZIA treated subjects who turned 18 years whilst participating in a study and tolerated a single highest dose of at least 1,000 mg peanut protein with no more than mild allergic symptoms at the exit DBPCFC (15/27, 55.6%) was consistent with the overall primary efficacy of the subjects aged 4 to 17 years.

Safety and efficacy in paediatric patients and in patients above 18 years

Efficacy and safety of Palforzia in children below 4 years and initiated in patients above 18 years has not yet been proven.

Long-term efficacy

Long-term efficacy has been demonstrated in 103 subjects and 26 subjects who completed 12 and 18 months respectively of PALFORZIA maintenance treatment with the ongoing therapeutic dose (300 mg daily) through participation in both PALISADE and the open-label, follow-on ARC004 study. A comparison of response rates after longer-term maintenance therapy with PALFORZIA can be made by comparing the response rates for the 12-month and 18-month maintenance cohorts in ARC004 with those who completed PALISADE (Table 8)**.**

Table 8: Percentage of Challenge Doses Tolerated Following Extended Maintenance During Exit DBPCFC (PALISADE and ARC004 Completer Populations, 4-17 Years)

	PALISADE	ARC004	
	6-month maintenance (N = 296)	**12-month maintenance (N = 103)**	**18-month maintenance (N = 26)**
Subjects who tolerated a single dose of peanut protein (response rate) [95% CI]			
2000 mg	na [1]	50 (48.5%) [38.6%, 58.6%]	21 (80.8%) [60.6%, 93.4%]
	187 (63.2%) [57.5%, 68.5%]	83 (80.6%) [71.6%, 87.7%]	25 (96.2%) [80.4%, 99.9%]
600 mg	250 (84.5%) [79.9%, 88.1%]	92 (89.3%) [81.7%, 94.5%]	25 (96.2%) [80.4%, 99.9%]
300 mg	285 (96.3%) [93.5%, 97.9%]	101 (98.1%) [93.2%, 99.8%]	26 (100%) [86.8%, 100.0%]

[1] 1,000 mg was the highest challenge dose of peanut protein in PALISADE.

Pharmacokinetics

No clinical studies investigating the pharmacokinetic profile and metabolism of PALFORZIA have been conducted. PALFORZIA contains naturally occurring allergenic peanut proteins. After oral administration, the proteins are hydrolysed to amino acids and small polypeptides in the lumen of the gastrointestinal tract.

Absorption

No data.

Distribution

No data.

Metabolism

No data.

Elimination

No data.

Preclinical data

No conventional preclinical studies on safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity have been performed.

Other Information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

The medicinal product may only be used until the date marked "EXP" on the container.

Special precautions for storage

Do not store above 25°C.
Keep out of reach of children.

Instructions for use

To empty the contents of each capsule, the two ends of the capsule should be pulled apart gently, and gently rolled between the finger and thumb. Sachets should be opened by carefully cutting or tearing along the line indicated.
After opening, gently tap the two halves of the capsule or sachet to ensure that all the powder is emptied.
Hands should be washed immediately after handling PALFORZIA capsule(s) or sachets.
Avoid inhaling the powder as this may worsen asthma or cause an allergic reaction.

PALFORZIA must not be added to food that has been heated above room temperature before consumption.
Ensure that PALFORZIA is consumed as soon as possible after it has been mixed with the food as much as possible.
The volume of the food should be such that the entire dose can be consumed in a few spoonfuls.
PALFORZIA should be consumed immediately after mixing, but can be mixed if necessary and refrigerated for up to 8 hours.

Marketing Authorisation Number

67733 (Swissmedic)

Content of Container

For medical use only – Pack for Initial Dose Escalation

2 capsules à 0.5 mg, 11 capsules à 1 mg (corresponds to 5 doses) [A]

Packs for up-Dosing:

Level 1 (3 mg):	48 capsules à 1mg (corresponds to 16 doses) [A]
Level 2 (6 mg):	96 capsules à 1 mg (corresponds to 16 doses) [A]
Level 3 (12 mg):	32 capsules à 1 mg, 16 capsules à 10 mg (corresponds to 16 doses) [A]
Level 4 (20 mg):	16 capsules à 20 mg (corresponds to 16 doses) [A]
Level 5 (40 mg):	32 capsules à 20 mg (corresponds to 16 doses) [A]
Level 6 (80 mg):	64 capsules à 20 mg (corresponds to 16 doses) [A]
Level 7 (120 mg):	16 capsules à 20 mg, 16 capsules à 100 mg (corresponds to 16 doses) [A]
Level 8 (160 mg):	48 capsules à 20 mg, 16 capsules à 100 mg (corresponds to 16 doses) [A]
Level 9 (200 mg):	32 capsules à 100 mg (corresponds to 16 doses) [A]
Level 10 (240 mg):	32 capsules à 20 mg, 32 capsules à 100 mg (corresponds to 16 doses) [A]
Level 11 (300 mg):	15 Sachets à 300 mg (corresponds to 15 doses) [A]

Packs for Maintenance Therapy:

30 sachets à 300 mg (corresponds to 30 doses) [A]

Marketing Authorisation holder

Medius AG, 4132 Muttenz

Date of information

November 2020