Swiss Summary of risk management plan for PALFORZIA

for

PALFORZIA®

(defatted powder of *Arachis hypogaea L.*, semen (peanuts))

Swiss RMP Summary
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The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of "Bezeichnung des Arzneimittels" is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of "Bezeichnung des Arzneimittels" in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. "Name of the marketing authorisation holder" is fully responsible for the accuracy and correctness of the content of the published summary RMP of "Bezeichnung des Arzneimittels.

Summary of risk management plan for PALFORZIA (defatted powder of *Arachis hypogaea L.*, semen (peanuts))

This is a summary of the risk management plan (RMP) for PALFORZIA. The RMP details important risks of PALFORZIA, how these risks can be minimised, and how more information will be obtained about PALFORZIA's risks and uncertainties (missing information).

PALFORZIA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how PALFORZIA should be used.

This summary of the RMP for PALFORZIA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of PALFORZIA's RMP.

I. The medicine and what it is used for

PALFORZIA is authorised for patients aged 4 to 17 years of age with a confirmed peanut allergy and may be continued in patients 18 years of age and older (see SmPC for the full indication). It contains defatted powder of *Arachis hypogaea L.,* semen (peanuts) as the active substance, and it is taken orally.

Further information about the evaluation of the benefit of PALFORZIA can be found in the EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/palforzia.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of PALFORZIA, together with measures to minimise such risks and the proposed studies for learning more about risks with PALFORZIA, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of PALFORZIA, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment – so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of PALFORZIA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of PALFORZIA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of PALFORZIA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Anaphylaxis/systemic allergic reactions Eosinophilic oesophagitis
Important potential risks	Possible rebound after discontinuation of treatment
Missing information	Use during pregnancy Impact on long-term immune-mediated reactions

II.B Summary of important risks

Important identified risk: Anaphylaxis/systemic allergic reactions	
Evidence for linking the risk to the medicine	Patients with peanut allergy may have allergic symptoms, including systemic allergic reactions, when treated with PALFORZIA as it contains defatted powder of *Arachis hypogaea L.*, semen (peanuts). *Systemic allergic reaction* is used to describe an anaphylactic reaction of any severity and *anaphylaxis* is used to describe an anaphylactic reaction that is severe. In the integrated safety population, systemic allergic reactions of any severity were reported in 15.1% of subjects, including 0.6% during initial dose escalation, 8.7% during up-dosing and 9.9% during m*ainte*nance. Severe systemic allergic reaction (anaphylaxis) was reported in 1.1% subjects, including 0.4% subjects during up-dosing and 0.8% during maintenance at 300 mg/day. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice.
Risk factors and risk groups	Patients are more likely to experience allergic symptoms in the presence of certain co-factors which are known to increase the likelihood of allergic reactions in general. These cofactors may be modifiable or non-modifiable. Modifiable co-factors may include exercise, hot bath or shower, alcohol consumption, fasting, or intake of non-steroidal anti-inflammatory medications. Non-modifiable co-factors may include intercurrent illness (eg, influenza or viral infection), an increase in severity of asthma, menstruation, stress, fatigue or sleep deprivation (Smith, 2015; Turner, 2017b; Varshney, 2009). In addition, patients aged 12 years or older and/or with high sensitivity to peanut may be at higher risk of experiencing allergic symptoms during treatment.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.2, SmPC section 4.3, SmPC section 4.4, and SmPC section 4.8*

	• *PL section 2, PL section 3, and PL section 4* • *Different dose levels distinguished through limiting the pack size and use of different coloured capsules* • *Prescription only medicine* Additional risk minimisation measures: • *Healthcare professional educational materials* • *Patient and parent/caregiver educational materials and Patient Card*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study ARC008 extension* • *Effectiveness evaluation of PALFORZIA educational materials* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: Eosinophilic oesophagitis (EoE)	
Evidence for linking the risk to the medicine	Eosinophilic oesophagitis is a significant allergic condition which if left untreated can cause lasting damage to the oesophagus. EoE has been reported for other OIT used to treat food allergies. In the integrated safety population, EoE was diagnosed in 5 of 944 subjects (0.5%) with a further 7 cases in other studies (1 subject in ARC001, 1 subject in ARC002, 1 subject in ARC004, and 4 subjects in ARC008) to total 12 of 1217 subjects (approximately 1%) treated with PALFORZIA experiencing EoE. After PALFORZIA was discontinued symptoms improved in all 12 subjects. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice. The published medical literature can support the evidence of a possible causal association based on what has been observed for other OIT and the predicted mechanism.
Risk factors and risk groups	A strong association between IgE-mediated food allergy and EoE has been observed (Greenhawt, 2014; Spergel, 2012). Consequently, patients with IgE-mediated food allergy who encounter the food to which they are allergic, either naturally or during OIT, are at increased risk of EoE. It remains unclear whether OIT induces EoE or causes pre-existing subclinical EoE to become symptomatic (Wright, 2018). The aetiology of EoE is multifactorial and unlike food anaphylaxis, which occurs in an estimated 15% of EoE patients (Assa'ad, 2007), patients with EoE are polysensitised to a variety of foods suggesting a general breakdown in oral antigen tolerance (Rothenberg, 2009). Male sex is a strong risk factor for EoE both in children and adults (Arias, 2016). Eosinophilic oesophagitis may occur at any age but there is a rising incidence in children with age and a peak in adults at 30-50 years with most cases occurring in children, adolescents, and adults younger than 50 years (Lucendo, 2017). A retrospective database analysis over a period of 8 years found that in 89 paediatric patients with EoE up to 18 years of age, male sex (78.6%), white race (94.4%), young age at diagnosis (mean ± SD, 6.2 ± 4.8 years), and atopy with sensitisation to

	environmental and food allergens in 79% and 75%, respectively, were prevalent (Assa'ad, 2007). The associated conditions extracted from the past medical history of the 89 patients or reported by the parents were atopy (asthma, allergic rhinitis, eczema, anaphylaxis to food, and allergic conjunctivitis in 39%, 30%, 19%, 9%, and 8%, respectively); immunologic (recurrent infections and autoimmune disorders in 13% and 2%, respectively); and developmental and neurologic (developmental delay, seizures, cerebral palsy, autism in 12%, 6%, 4%, and 1%); and chromosomal abnormalities in 1% patients (Assa'ad, 2007). EoE patients usually suffer from a high number of concomitant atopic disorders including rhinitis, asthma and eczema. A recent systematic review of 21 studies comprising 53,542 EoE patients and 54,759 controls found that allergic rhinitis was significantly more common among patients with EoE compared with control subjects as were bronchial asthma and eczema (González-Cervera, 2017). Eosinophilic oesophagitis has a strong familial association (Rothenberg, 2009). Nearly 10% of parents of EoE patients have a history of oesophageal strictures and an estimated 8% have biopsy proven EoE (Noel, 2004). In a study out of the 103 paediatric patients 73.5% had a family history of atopic disease, 6.8% a family history of EoE, 9.7% a family history of oesophageal dilatation, 57.4% rhinoconjunctivitis, 36.8% wheezing, and 46% possible food allergy (Noel, 2004).
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.3, SmPC section 4.4, and SmPC section 4.8* • *PL section 2 and PL section 4* Additional risk minimisation measures: • *Healthcare professional educational materials* • *Patient and parent/caregiver educational materials*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study ARC008 extension* • *Effectiveness evaluation of PALFORZIA educational materials* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Possible rebound after discontinuation of treatment	
Evidence for linking the risk to the medicine	When PALFORZIA treatment is discontinued an increased severity of allergic reactions (ie, rebound) upon exposure to peanut could possibly occur compared with the severity of allergic reactions before or during treatment. However, this is very unlikely due to the competitive inhibition by IgG4 of antigen binding to IgE (Kulis, 2018; Vickery, 2013; Jones, 2009) and that the effects of IgE elevation have not been observed to result in rebound or exacerbated effects after discontinuation of treatment. For patients who discontinued the clinical studies early, no systemic allergic reaction events, accidental exposures to peanut, or other important safety events were reported in any of the follow-up periods. A search of the published literature found no reports that suggest an increased risk of increased severity of reactions (ie, rebound)

	following discontinuation of food OIT at any point during the process. Clinical trials can provide an estimation of the frequency and nature of an adverse reaction that is expected to occur in clinical practice. The published medical literature can support the evidence of a possible causal association based on what has been observed for other OIT and the predicted mechanism.
Risk factors and risk groups	There are no known risk factors that increase possible rebound after discontinuation of treatment. The risk factors that increase the likelihood of anaphylaxis/ systemic allergic reactions are described for the important identified risk anaphylaxis/systemic allergic reactions.
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.2* • *PL section 3* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study ARC008 extension* See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Use during pregnancy	
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.6* • *PL section 2* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Post-marketing pregnancy registry* See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Impact on long-term immune-mediated reactions	
Risk minimisation measures	Routine risk minimisation measures: • *SmPC section 4.2* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *Study ARC008 extension* See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of PALFORZIA.

II.C.2 Other studies in post-authorisation development plan

Study ARC008: Open-label extension for maintenance of desensitization and safety

Purpose of the study: Additional data on maintenance of desensitization and safety on longer-term treatment with PALFORZIA is needed.

The objectives of the study are to evaluate safety and tolerability, maintenance of desensitization, and effects on immunologic parameters after longer-term administration of PALFORZIA and follow-up observation after treatment discontinuation.

Post-marketing pregnancy registry

Purpose of the study: To collect, analyse, and report data on pregnancy outcomes and infant outcomes after exposure to PALFORZIA during pregnancy

Effectiveness evaluation of PALFORZIA educational materials

Purpose of the study: The key study objectives are to evaluate:

- Healthcare professional's understanding and retention of core educational material messages
- Parent/caregiver's (4-11 year old patients) understanding and retention of core educational messages
- Patient's (12-17 year old) understanding and retention of core educational messages
- Monitor adherence to educational materials distribution plan

List of references in the Summary of the RMP

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