NCPE Assessment

Technical Summary

Defatted powder of *Arachis hypogaea L.*, semen (peanuts) (Palforzia®)

HTA ID: 22019

November 2023

Applicant: Aimmune Therapeutics Ireland Limited

Palforzia® for the treatment of patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. Palforzia® may be continued in these patients when they reach 18 years of age.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of Defatted powder of *Arachis hypogaea L.* semen (peanuts) (Palforzia®).

Following assessment of the Applicant's submission, the NCPE recommends that Palforzia® not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Aimmune Therapeutics Ireland Limited) Health Technology Assessment of Defatted powder of *Arachis hypogaea L.* semen (peanuts) (Palforzia®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In January 2023, Aimmune Therapeutics Ireland Limited submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of defatted powder of *Arachis hypogaea L.,* semen (peanuts) (Palforzia®), for the treatment of patients aged 4 to 17 years with a confirmed diagnosis of peanut allergy. Palforzia® may be continued in these patients when they reach 18 years of age. Aimmune Therapeutics Ireland Limited is seeking reimbursement on the Community Drug Schemes.

Palforzia® is an allergen-specific immunotherapy. Allergen specific immunotherapy is an approach where increasing amounts of an allergen are administered to patients with immunoglobulin E mediated allergy to raise the threshold and decrease the severity of allergic responses. The precise mechanism of desensitisation provided by Defatted powder of *Arachis hypogaea L., semen* (peanuts) is not fully understood. Palforzia® is an oral powder in capsules for opening or in sachets. The powder should be taken after mixing with an age-appropriate soft food.

Palforzia® should be administered under the supervision of a health care professional qualified in the diagnosis and treatment of allergic diseases. Treatment is administered in three sequential phases; initial dose escalation (IDE), up-dosing and maintenance. IDE is administered on a single day. The IDE dosing schedule is 0.5mg, 1mg, 1.5mg, 3mg, and 6mg with all doses separated by an observation period of 20 to 30 minutes and no dose level omitted. Up-dosing is initiated the day after IDE. During up-dosing, the following once daily doses should be administered for two weeks each in the sequential order: 3mg, 6mg, 12mg, 20mg, 40mg, 80mg, 120mg, 160mg, 200mg, 240mg, 300mg. Temporary dose modification may be required during the up-dosing phase. This may involve holding the dose level for longer than two weeks, reducing, or withholding doses. IDE and the first dose of each new up-dosing level are to be administered in a health care setting prepared to manage potential severe allergic reactions. All dose levels of up-dosing must be completed before starting maintenance. The maintenance dose is 300mg once daily (equivalent to the protein content of approximately one peanut kernel). Daily maintenance is required to maintain tolerability and clinical effects of Palforzia®. Palforzia® should be used in conjunction with a peanut-

avoidant diet. Efficacy data are available for up to 24 months of treatment; the product licence makes no recommendation about the duration of treatment beyond 24 months.

The comparator for this Health Technology Assessment is peanut avoidance.

1. Comparative effectiveness of **Palforzia®**

PALISADE, was an international, randomised, double-blind, placebo-controlled trial designed to study the safety and efficacy of Palforzia®. The trial recruited participants aged 4 to 55 years, however only results for the licensed population (4 to 17 years) are presented below. Participants underwent a Screening double-blind placebo-controlled food challenge (DBPCFC). Those with an allergic response to 100mg or less of peanut protein were randomly assigned 3:1 to receive Palforzia® or placebo. All participants maintained peanut avoidance. Participants were followed for approximately 12 months overall. The up-dosing period varied depending on tolerated dose (20 to 40 weeks) and patients were then followed for six months of maintenance therapy. The primary endpoint was the proportion of participants, aged 4 to 17 years, who achieve desensitisation as determined, at an Exit DBPCFC, by tolerating a single highest dose of at least 1000 mg (equivalent to 2043 mg cumulative dose given during the Exit DBPCFC process) of peanut protein with no more than mild symptoms. Participants without an Exit DBPCFC were classified as non-responders.

In PALISADE, 750 individuals, aged 4 to 17 years, were screened and 555 eligible participants underwent randomisation. The median age was 9 years, 57.2% were male, and were predominantly white (79.5%). The majority had a history of peanut anaphylaxis (72%), asthma (53%), and multiple food allergies (66%). The proportion who tolerated at least 1000 mg of peanut protein (cumulative dose 2043 mg), at Exit DBPCFC, with no more than mild symptoms was 50.3% in the Palforzia® arm compared with 2.4% in the placebo arm; treatment difference: 47.8% (95% CI 38.0% to 57.7%; $p < 0.0001$).

A total of 256 participants in the Palforzia® arm who tolerated at least 300mg peanut protein in the PALISADE Exit DBPCFC, enrolled in the open-label extension study, ARC004. Among those who continued to receive 300mg Palforzia® daily as maintenance treatment, 48.5% (95% CI 38.6% to 58.6%) and 80.8% (95% CI 60.6% to 93.4%) tolerated the highest challenge

dose of 2000 mg of peanut protein in the completer populations of Cohort 1 (n=103, approximately 18 months of continuous treatment) and cohort 3a (n=26, approximately 24 months of continuous treatment), respectively.

A second pivotal, randomised, double-blind, placebo-controlled trial, ARTEMIS, was conducted in a European population only. Overall, ARTEMIS was similar in design to PALISADE with some exceptions. The eligible age was restricted to 4 to 17 years. Also, participants were required to have an allergic response at a Screening DBPCFC of 300mg or less of peanut protein. This resulted in a less sensitive population compared to that of PALISADE. In ARTEMIS, 227 participants were screened in which 175 were randomised to receive either Palforzia® (n=132) or placebo (n=43). Efficacy results were in line with those in the PALISADE trial.

The Review Group note the following:

- The tolerated dose in DBPCFC does not predict the amount of peanut protein that could be tolerated in real life, as other factors can impact the severity of reactions.
- There is no direct clinical evidence that Palforzia® reduces the frequency and severity of reactions to accidental peanut exposure.
- The treatment effect of Palforzia® beyond two years is unknown.
- The effect of stopping treatment and transitioning to regular inclusion of peanuts in the diet has not been investigated in the trials nor addressed in the product licence.
- Treatment is not curative. The product licence states that Palforzia® should be used in conjunction with a peanut-avoidant diet.

2. Safety of **Palforzia®**

The most common adverse reactions (of any severity) are reported to be abdominal pain (49.4%), throat irritation (40.7%), pruritus (33.7%), nausea (33.2%), vomiting (28.5%), urticaria (28.5%), oral pruritus (26.0%), abdominal discomfort (22.9%), and abdominal pain upper (22.8%). The incidence of adverse reactions was more common in the up-dosing phase (85.7% of participants) compared with the IDE phase (45.1%) and maintenance phase (57.7%). Anaphylactic reactions occurred in 15.1% of participants; including 0.6% during IDE, 8.7% during up-dosing, and 9.9% during maintenance. Severe systemic allergic reactions

(anaphylaxis) was reported in ten participants (1.1%). Eosinophilic oesophagitis was identified as the second most important safety risk associated with treatment, occurring in 1% of participants.

Allergic reactions to Palforzia® are expected; the majority of reactions are mild to moderate, but reactions can be life-threatening. Patients, or carers, must carry self-injectable adrenaline at all times. Treatment interruptions, including non-daily dosing, may potentially lead to an increased risk of allergic reactions and anaphylaxis.

3. Cost effectiveness of **Palforzia®**

Methods

A cohort-level Markov model comprised health states based on treatment status (up-dosing, maintenance), maximum tolerated dose (MTD) of peanut protein (<300mg, 300mg, 600mg, 1000mg, 2000mg), 'peanut in diet' (i.e. regular peanuts in diet in order to maintain desensitisation), spontaneous tolerance and death. All patients in the model follow a peanut-avoidant diet apart from those in the 'peanut in diet' and 'spontaneous tolerance' health states. Those who transition to 'MTD <300mg' at any stage remain here for life. Higher MTD states are associated with higher utilities and fewer reactions to accidental peanut exposure. The state associated with the highest utility and lowest cost (i.e. 'peanut in diet') is only available to those in the Palforzia® arm. The model population, informed by the PALISADE trial, consists of those aged 4 to 17 years with confirmed peanut allergy.

Treatment effectiveness was captured via MTD (as measured by a food challenge). Treatment -specific transition probabilities between the MTD-based health states were primarily sourced from PALISADE and ARC004. After two years of treatment with Palforzia®, patients with an MTD of at least 300mg, can discontinue and transition to the 'peanut in diet' health state. Patients who do not discontinue at this timepoint remain on Palforzia® treatment for life. In the following year, a one-off transition from 'peanut in diet' to 'MTD <300mg' health state is possible. Transitions to and from the 'peanut in diet' state were informed by a structured expert elicitation exercise conducted with eight clinical experts. These transitions were not supported by the Palforzia® clinical trial evidence nor the product licence.

Utilities were informed by a vignette-based utility study conducted among patients and carers (of patients who were aged 4 to 17 years). Pooled data from this study (collected via an online survey or an online structured interview) was used in the model. The study was poorly reported with minimal detail given on the methods used. The utility difference between the 'MTD <300mg' health state (where the majority of patients in the peanut avoidance only arm lie) and the 'peanut in diet' health state (which only patients in the Palforzia® arm may enter) is a key model driver.

The Review Group had a number of concerns:

- The assumption, that the majority of patients discontinue Palforzia® following two years of treatment (and include regular peanut in their diet) and that the remainder stay on treatment for life, is informed by a structured expert elicitation exercise. This is not in line with the product licence nor is it supported by clinical trial evidence.
- The treatment benefit is mainly derived from differences in utility values between the 'MTD <300mg' and the 'peanut in diet' health states. These utility values are highly uncertain.
- A key clinical outcome of Palforzia® treatment (frequency and severity of reactions due to accidental exposure to peanut) does not have a major impact on the cost-effectiveness results.
- The service setup costs have not been accounted for.

Owing to the model structure and lack of available evidence, it was not possible to address these concerns in the NCPE adjusted base case. The Review Group had several concerns with the conduct of the expert elicitation exercise. In particular, there was inadequate justification on why the value chosen (83%) for the proportion of patients that switch to peanuts in diet, after completing two years of treatment, was based on the judgement of one individual expert. In the NCPE adjusted base case, the Review Group equally weighted the judgements of all experts by using a value that was based on the pooled group distribution (78.4%). Also, utilities from the online survey, consisting of both adolescent self-reports and carer-proxy reports, were used (rather than the pooled data). However, these utilities remain uncertain. Health-related quality of life impacts (associated with up-dosing, maintenance, and food challenge tests) in the placebo arm were removed as these events

would not occur, in the real world setting, in individuals who were not receiving Palforzia®.

Results

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the NCPE adjusted base case and the Applicant's base case assumptions are shown in Table 1 and Table 2, respectively. In both the NCPE and Applicant base cases, the magnitude of the associated QALY gain cannot be adequately quantified; thus the ICERs are highly uncertain.

Table 1: NCPE adjusted base case incremental cost-effectiveness results*

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Peanut avoidance	13,005	17.788	-	-	-
Palforzia®	42,331	18.346	29.236	0.558	52,571

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. Costs and outcomes are discounted at 4%.
* Corresponding probabilistic ICER using 5000 iterations =€53,241/QALY. Figures in the table are rounded, and so calculations may not be directly replicable

Table2: Applicant base case incremental cost-effectiveness results*

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
Peanut avoidance	13,005	17.709	-	-	-
Palforzia®	38,587	18.389	25,582	0.680	37,616

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year. Costs and outcomes are discounted at 4%.
* Corresponding probabilistic ICER using 5,000 iterations =€39,747/QALY. Figures in the table are rounded, and so calculations may not be directly replicable

Sensitivity analysis

Under the NCPE adjusted base case, the probabilities of cost-effectiveness at a willingness-to pay threshold of €20,000 per quality-adjusted life year (QALY) and €45,000 per QALY were 6% and 43%, respectively. Under the Applicant's assumptions, the respective probabilities were 11% and 59%. Given the limitations of the model, the probabilities of cost effectiveness, in both the NCPE and Applicant base cases, fail to reflect the full extent of uncertainty.

Under the NCPE-adjusted base case assumptions, the Review Group estimate that price reductions of approximately 81% and 25% would be required to achieve cost-effectiveness at the €20,000 per QALY and €45,000 per QALY thresholds, respectively. However, this

estimate is highly sensitive to the assumptions on the proportion of patients that transition to 'peanut in diet' and the choice of utilities.

A scenario, of the NCPE adjusted base case, where no patients transition to 'peanut in diet' (and instead remain on Palforzia® for life), resulted in an ICER of €128,368 per QALY (incremental QALY: 0.692, incremental cost: €88,767). This scenario investigates the impact of the highest expected drug acquisition cost. However, the ICER remains uncertain given the highly uncertain utilities.

4. Budget impact of **Palforzia®**

Palforzia® is flat-priced across daily doses. The price-to-wholesaler, per daily dose of Palforzia®, is €12.79. Assuming a relative dose intensity of 98% (in line with the PALISADE trial), the total cost per patient per year (including all relevant fees and a Framework agreement rebate of 8.5%), is €4,753 per patient for the first year of treatment and €4,716 per year thereafter.

The Applicant assumes that there are currently two centres having the necessary infrastructure in place to initiate treatment with Palforzia®. Each centre is assumed to initiate 150 patients per year. Accounting for discontinuations, the Applicant predicts 269 patients will be treated in Year 1 increasing to 641 patients in Year 5. Assuming that 78.4% of patients on treatment at the end of Year 2 discontinue Palforzia® and start including regular peanut in their diet, the cumulative five-year gross drug-budget impact is an estimated €12.3 million. This assumption is not supported by the product licence or clinical trial evidence. Consequently, budget impact estimates are highly uncertain

Non-drug costs considered include resource use costs (including administration and supervision) as well as cost-offsets arising from less treatments for reactions to accidental peanut exposure. The five-year cumulative net budget impact is €18.11 million. This analysis does not account for service setup costs.

5. Patient Organisation Submission

A patient group submission was received.

6. Conclusion

The NCPE recommends that Palforzia® not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.*