PDL DRUG REVIEW

Proprietary Name: Palforzia®
Common Name: peanut (*Arachis hypogaea*) allergen powder-dnfp
PDL Category: Allergenic Extracts

Summary

Pharmacology/Usage: Palforzia® (peanut [*Arachis hypogaea*) allergen powder-dnfp) is a powder for oral administration manufactured from defatted peanut flour. It is an oral immunotherapy but the exact mechanism of action has not been established.

Indication: For the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Palforzia® is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial dose escalation may be administered to patients aged 4 through 17 years. Up-dosing and maintenance may be continued in patients 4 years of age and older.

Palforzia® is to be used in conjunction with a peanut-avoidant diet. It is not indicated for the emergency treatment of allergic reactions, including anaphylaxis.

There is no pregnancy category for this medication; however, the risk summary indicates that no human or animal data are available to establish the presence or absence of the risks due to Palforzia® in pregnant women. There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Palforzia® during pregnancy. Women exposed during pregnancy or their health care professionals are encouraged to contact Aimmune by calling 1-833-246-2566. The safety and efficacy of use in the pediatric population younger than 4 years of age have not been established.

Dosage Form: To include the following:

- Fine powder (may contain clumps) in capsules: 0.5mg, 1mg, 10mg, 20mg, 100mg. Do not swallow capsules.
- Fine powder (may contain clumps) in foil-laminate sachets: 300mg. Do not inhale powder.

Each dose meets specifications for quantities of Ara h 1 (peanut seed storage protein), Ara h 2 (commonly recognized peanut component by IgE), and Ara h 6 (major peanut allergen similar to Ara h 2), measured by immunoassay alone or in combination with high performance liquid chromatography.

Recommended Dosage: Verify the patient has injectable epinephrine prior to initiation and during therapy and instruct patients on its appropriate use.

Treatment with Palforzia® is administered in 3 sequential phases, including the Initial Dose Escalation, Up-dosing, and Maintenance. Initial dose escalation is administered on a single day under the supervision of healthcare provider in a healthcare setting with the ability to manage potentially severe allergic reactions, including anaphylaxis. Initial Dose Escalation is administered in sequential order on a single day beginning at Level A (5 Levels A-E, 0.5-6mg; see table in prescribing information). Each dose should be separated by an observation period of 20-30 minutes, and no dose level should be omitted. Observe patients after the last dose for at least 60 minutes until suitable for discharge. Discontinue treatment if symptoms requiring medical intervention occur with any dose during Initial Dose Escalation. Patients who tolerate at least the 3mg single dose (Level D) of Palforzia® during Initial Dose Escalation must return to the healthcare setting for initiation of Up-Dosing. If possible, Up Dosing should be done the day after Initial Dose Escalation. Repeat Initial Dose Escalation in a healthcare setting if the patient is unable to have Up Dosing done within 4 days.

Complete Initial Dose Escalation before starting Up Dosing. Up Dosing consists of 11 dose levels and is started at a 3mg dose. The first dose of each new Up Dosing level is administered under the supervision of a healthcare provider. Observe patients after administering the first dose of a new Up Dosing level for at least 60 minutes until suitable for discharge. If the patient tolerates the first dose of the increased dose level, the patient may continue that dose level at home. Each dose should be consumed daily with a meal at about the same time each day, preferably in the evening. Administer all the dose levels (see Table in prescribing information) in sequential order at 2-week intervals if tolerated, and no dose level should be omitted. No more than one dose should be consumed per day; however, consider dose modification or discontinuation for patients who do not tolerate Up Dosing as per the prescribing information.

Complete all dose levels of Up Dosing before starting Maintenance. The daily dosing configuration for maintenance is 300mg daily. Daily maintenance is required to maintain the effect of Palforzia®. During maintenance, contact patients at regular intervals to assess for adverse reactions.

Open capsules(s) or sachet and empty the entire dose of Palforzia® powder onto a few spoonfuls of refrigerated or room temperature semisolid food (e.g. applesauce, yogurt, pudding). Do not use liquid (e.g. milk, water, juice) to prepare. Mix well and consume the entire volume of the prepared mixture promptly. Dispose of the opened capsule(s) or sachet and wash hands immediately after handling Palforzia®.

Discontinue treatment with Palforzia® for:

- Patients who are unable to tolerate doses up to and including the 3mg dose during Initial Dose Escalation
- Patients with suspected eosinophilic esophagitis
- Patients unable to comply with the daily dosing requirements
- Patients with recurrent asthma exacerbations or persistent loss of asthma control

Drug Interactions: There are no drug interactions listed with this product.

Box Warning: Palforzia® has a box warning regarding anaphylaxis, which may be life-threatening. Anaphylaxis can occur at any time during Palforzia® treatment. Providers should prescribe injectable epinephrine and educate patients on appropriate use. Do not administer Palforzia® to patients with uncontrolled asthma. Dose modifications may be needed after an anaphylactic reaction. Furthermore, observe patients during and after administration of the Initial Dose Escalation and the first dose of each Up Dosing level, for at least 60 minutes. Due to the risk of anaphylaxis, Palforzia® is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Palforzia® REMS.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Palforzia® 300g) minus reported % incidence for placebo in study 1. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included abdominal pain (12.1%), vomiting (4.2%), nausea (7.7%), oral pruritus (10.6%), oral paresthesia (5.7%), throat irritation (4.6%), cough (1.1%), rhinorrhea (7.2%), sneezing (6.4%), throat tightness (6.5%), wheezing (0%), dyspnea (4.7%), pruritus (2.6%), urticaria (5.9%), anaphylactic reaction (7%), and ear pruritus (2.3%).

See box warning section as anaphylaxis has been reported during all phases of Palforzia® dosing. Do not initiate Palforzia® treatment in a patient who has had severe or life-threatening anaphylaxis within the previous 60 days. Palforzia® may not be suitable for patients with certain medical conditions that may reduce the ability to survive anaphylaxis, including but not limited to markedly compromised lung function, severe mast cell disorder, or cardiovascular disease. Palforzia® may not be suitable for patients taking medications that can inhibit or potentiate the effects of epinephrine. As Palforzia® can cause anaphylaxis, which may be life-threatening, it is only available through a restricted REMS. Requirements of the Palforzia® REMS include the following:

- Health care providers who prescribe Palforzia® must be certified with the program by enrolling
- Healthcare settings must be certified, have on-site access to equipment and personnel trained to manage anaphylaxis, and establish policies and procedures to verify that the patients are monitored
- Patients must be enrolled prior to the start of treatment and must be informed of the need to have injectable epinephrine available for immediate use at all times

- Pharmacies must be certified with the program and only dispense Palforzia® to healthcare settings that are certified or to patients who are enrolled depending on the treatment phase.

Uncontrolled asthma is a risk factor for a serious outcome, including death, in anaphylaxis. Ensure patients have their asthma under control prior to the start of Palforzia®.

In clinical studies, 28 of 1050 (2.7%) of subjects were referred for a gastroenterology evaluation and 17 of these 28 subjects reported undergoing an esophagogastroduodenoscopy (EGD). Of those who underwent an EGD, 12 were diagnosed with biopsy-confirmed eosinophilic esophagitis while receiving Palforzia® compared with 0 receiving placebo. Discontinue Palforzia® and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent GI symptoms, including dysphagia, vomiting, nausea, GERD, chest pain, or abdominal pain.

Contraindications: In patients with uncontrolled asthma and in patients with a history of eosinophilic esophagitis and other eosinophilic gastrointestinal disease.

Manufacturer: Aimmune Therapeutics

Analysis: The efficacy of Palforzia® for the mitigation of allergic reactions was assessed in a phase 3, randomized, double-blind, multicenter, placebo-controlled trial that included patients with peanut allergy aged 4 through 55 years. The primary analysis population consisted of 496 subjects aged 4 through 17 years of age in the intent-to-treat population who received at least 1 dose of study treatment. Patients went through an Initial Dose Escalation and underwent Up Dosing for 20-40 weeks until the maintenance 300mg dose was reached. Subjects underwent 24-28 weeks of maintenance immunotherapy until the end of the study. At the end of the maintenance period, subjects completed an exit double-blind, placebo-controlled, food-challenge (DBPCFC) to approximate an accidental exposure to peanut and to assess their ability to tolerate increasing amounts of peanut protein with no more than mild allergic symptoms.

The primary outcome was the percentage of subjects tolerating a single dose of 600mg peanut protein in the exit DBPCFC with no more than mild allergic symptoms after 6 months of maintenance treatment. The primary endpoint was considered met if the lower bound of the 95% confidence interval for the difference in response rates between the treatment and placebo groups was greater than the prespecified margin of 15%. Key secondary endpoints included the comparisons of the response rates after single doses of 300mg and 1000mg peanut protein as well as a comparison of the maximum severity of symptoms at any challenge dose of peanut protein during the exit DBPCFC. The key secondary outcomes were assessed for statistical significance only if the primary endpoint and all the preceding tests in the hierarchy were statistically significant in favor of Palforzia®. Response rates at the exit DBPCFC, which included the ITT population 4 through 17 years of age, can be seen in the table below, which was adapted from the prescribing information.

Peanut challenge dose, single dose	300mg	600mg	1000mg
Palforzia® (N=372)	76.6%	67.2%	50.3%
Placebo (N=124)	8.1%	4.0%	2.4%
Treatment difference	68.5%	63.2%	47.8%
p-value	<0.0001	<0.0001	<0.0001
NNT calculated by CHC	2	2	3

The completer population consisted of all subjects aged 4 through 17 years in the ITT population who stayed on treatment and had an evaluable exit DBPCFC (N=296 Palforzia®, N=116 placebo). In the completer population, the proportion who tolerated single highest doses of 300mg, 600mg, and 1000mg with no more than mild symptoms at the exit DBPCFC were 96.3%, 84.5%, and 63.2%, respectively for Palforzia®-treated subjects compared with 8.6%, 4.3%, and 2.6% for placebo-treated subjects. The table below includes the data on the maximum severity of symptoms at any challenge dose during the exit DBPCFC in the ITT population for ages 4 through 17.

Symptom Severity	Palforzia® (N=372)	Placebo (N=124)
None	37.6%	2.4%
Mild	32.0%	28.2%
Moderate	25.3%	58.9%
Severe	5.1%	10.5%

There are no data available on the efficacy of Palforzia® in subjects who did not progress onto maintenance therapy.

Place in Therapy: Palforzia® is an oral immunotherapy indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Palforzia® is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial Dose Escalation may be administered to patients aged 4 through 17 years. Up Dosing and Maintenance may be continued in patients 4 years of age and older. Palforzia® is to be used in conjunction with a peanut-avoidant diet. Palforzia® is not indicated for the emergency treatment of allergic reactions, including anaphylaxis. There is a box warning listed with Palforzia®, warning of the risk of anaphylaxis, which can be life-threatening and can occur at any time during Palforzia® therapy. Due to this risk, Palforzia® is available only through a restricted program under a REMS called the Palforzia® REMS. This is the first therapy approved for peanut allergy. In a large study, the use of peanut allergen-dnfp compared with placebo resulted in a significantly greater number of patients able to ingest a single-dose of 600mg of peanut protein during the exit food challenge in patients 4 to 17 years of age with no more than mild symptoms, but not among patients 18 to 55 years of age. Per the full-text article by Vickery et al,[2] "Efficacy was not shown in the participants 18 years of age or older."

It is recommended that Palforzia® should be non-preferred and require prior authorization in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement:

- ☐ **Preferred**
- ☒ **Non-Preferred**
- ☒ **Refer to DUR for PA Criteria**

References

[1] Palforzia [package insert]. Brisbane, CA: Aimmune Therapeutics, Inc; 2020.
[2] Vickery BP, Vereda A, Casale TB, et al. AR101 oral immunotherapy for peanut allergy. NEJM. 2019; 379(21): 1991-2001.