

**Date:** January 29, 2020

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**BLA STN#:** 125696

**Applicant Name:** Aimmune Therapeutics, Inc.

**Date of Submission:** December 21, 2018

**Products:** Palforzia, [Peanut (*Arachis hypogaea*) Allergen Powder-dnfp]  
powder for oral administration

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

- (A) The estimated size of the population likely to use the drug involved;
- (B) The seriousness of the disease or condition that is to be treated with the drug;
- (C) The expected benefit of the drug with respect to such disease or condition;
- (D) The expected or actual duration of treatment with the drug;
- (E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
- (F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of Vaccines Research and Review and the Office of Biostatistics and Epidemiology, we have determined that a REMS that includes elements to assure safe use (ETASU) is necessary for Palforzia to ensure that the benefits of the drug outweigh the risk of anaphylaxis.

During the pre-market evaluation of this application, Palforzia recipients 4 through 17 years of age reported an increased frequency of anaphylaxis compared to placebo

recipients (14.2% vs. 3.2%, respectively). Such an imbalance in the frequency of anaphylaxis was observed during Initial Dose Escalation, Up-Dosing, and Maintenance dosing. Furthermore, Palforzia recipients reported use of epinephrine to treat allergic reactions more frequently than placebo recipients (14.0% vs. 6.5%, respectively). Epinephrine was administered both in the clinic by the investigators during the Initial Dose Escalation and Up-Dosing visits, as well as by patients/caregivers throughout the study. Among Palforzia recipients who were administered epinephrine in a healthcare setting, epinephrine use occurred more frequently during Up-Dosing than during Maintenance (18 vs. 3 episodes). This finding suggests that Palforzia recipients are at higher risk for anaphylaxis when they take the first dose of Up-Dosing levels than when they take Maintenance doses. It is important to note that patients with IgE-mediated food allergy are routinely advised to treat themselves with injectable epinephrine at the first sign(s) of an allergic reaction to prevent progression to a more severe reaction. However, many peanut-allergic patients do not have epinephrine available to treat a reaction. One published study noted that only 43% of peanut allergic patients  $\leq 18$  years of age had injectable epinephrine available to treat a reaction [1].

Due to the risk of anaphylaxis, which will be included in a boxed warning on the Prescribing Information (PI), ETASU A, ETASU B, ETASU C, ETASU D, and ETASU E will be required to ensure that the drug's benefits outweigh the risks. The REMS for Palforzia requires that healthcare providers who prescribe and healthcare settings that dispense and administer Palforzia are certified and educated on: a) the risk of anaphylaxis associated with the use of Palforzia and b) the requirement that Initial Dose Escalation and the first dose of each Up-Dosing level must only be administered to patients in a healthcare setting equipped to monitor patients, and to identify and manage anaphylaxis. The REMS requires that Initial Dose Escalation and the first dose of each Up-Dosing level are only administered to patients in certified healthcare settings. The REMS also requires that Palforzia is only dispensed and administered to patients who are informed of the need to have injectable epinephrine available for immediate use, the need for monitoring after the Initial Dose Escalation and first dose of each Up-Dosing level, and the need for continued dietary peanut avoidance.

Healthcare providers who prescribe Palforzia must become certified by enrolling in the REMS program. Healthcare providers who prescribe Palforzia must enroll patients in the REMS program, counsel patients (or their parents or guardians) on the safe use of Palforzia, assess the patient's supply of injectable epinephrine, and assess the patient's tolerability of previous Up-Dosing levels and appropriateness of continuing the Up-Dosing. Patients who are prescribed Palforzia must enroll in the REMS program before initiating treatment. Patients must receive counseling on the safe use of Palforzia and how to recognize the signs and symptoms of anaphylaxis, and must attest to having injectable epinephrine available for immediate use and to avoid peanut in the diet. Healthcare settings that dispense Palforzia must become certified by enrolling in the REMS program; have healthcare provider(s) on-site to monitor for and manage anaphylaxis; be able to manage anaphylaxis on-site; train staff involved in dispensing and administering Palforzia; verify that patients have injectable epinephrine; and establish processes and procedures to verify that patients are monitored by a

healthcare provider during and after the Initial Dose Escalation and the first dose of each Up-Dosing level, when patients are at highest risk for anaphylaxis. Pharmacies must become certified to dispense Palforzia by enrolling in the REMS program. Pharmacies that dispense Palforzia must train all relevant staff and establish processes and procedures to verify: prescriber certification, patient enrollment, dispensing of Initial Dose Escalation doses only to certified healthcare settings, and dispensing only one Up-Dosing dose level at a time to a patient. Wholesalers-distributors will distribute Palforzia only to certified pharmacies and healthcare settings.

In reaching this determination, we considered the following:

- A: The estimated number of pediatric patients in the United States with IgE-mediated peanut allergy is about 1 million [2]. The prevalence of peanut allergy in children in the United States is about 1-2% and has been increasing from 1997 (0.4%) to 2008 (1.4%) [3]. Only about 20% of children outgrow a peanut allergy [4]. This estimate is based on claims from healthcare databases, surveys/questionnaires, allergy testing and oral food challenges to peanut. While Palforzia is contraindicated for use in peanut allergic patients with uncontrolled asthma and eosinophilic gastrointestinal disease, these are uncommon conditions and the majority of peanut allergic patients 4 through 17 years of age will be eligible for Palforzia therapy.
- B: IgE-mediated peanut allergy is a serious, life-threatening condition. There are no approved therapies to reduce the incidence of reactions in the event of accidental exposure to peanut. Instead, injectable epinephrine and/or antihistamines are used to treat and prevent the progression of an allergic reaction. Even with immediate treatment of allergic symptoms with epinephrine, these reactions have resulted in fatalities. Quality of life in patients and their caregivers is often adversely affected due to the fear of accidental ingestion due to undeclared allergens as well as the burden of avoiding allergenic foods [5].
- C: The pre-specified primary efficacy endpoint in the phase 3 study was the proportion of subjects 4 through 17 years of age who tolerated a single dose of 600 mg of peanut protein at an exit double-blind placebo-controlled food challenge (DBPCFC) after 6 months of Maintenance treatment. The success criterion was met if the lower bound of the 95% CI for the treatment difference between Palforzia and placebo was greater than 15%. This criterion was met with a treatment difference (efficacy) estimate of 63.2% (95% CI: 53.0, 73.3). In addition, Palforzia recipients demonstrated a strong treatment effect and dose-response to 300 mg and 1000 mg of peanut protein during a DBPCFC after Palforzia treatment as well as a reduction in the overall severity of allergic symptoms during a DBPCFC when compared to placebo recipients.
- D: Treatment with Palforzia is administered in three sequential phases: Initial Dose Escalation, Up-Dosing, and Maintenance. Initial Dose Escalation is administered on a single day. Up-Dosing consists of 11 dose levels, with sequential increases in dose every two weeks, as tolerated. Maintenance is started after completion of all

dose levels of Up-Dosing. Daily Maintenance doses are required to maintain the effect of Palforzia.

- E: As discussed in the introduction, in a clinical trial, Palforzia recipients 4 through 17 years of age reported an increased frequency of anaphylaxis compared to placebo recipients (14.2% vs. 3.2%, respectively). In the same clinical trial, Palforzia recipients reported use of epinephrine as a rescue medication to treat allergic reactions more frequently compared to placebo recipients (14.0% vs. 6.5%, respectively). Gastrointestinal disorders, most of which were allergic in nature, were the most commonly reported adverse reactions in Palforzia recipients. A total of 12 cases of eosinophilic esophagitis were reported in 1050 Palforzia recipients (1.1%) with zero reports in placebo recipients. No deaths were related to Palforzia. The frequency of serious adverse events (SAEs) in the clinical study was low (2.2% in Palforzia recipients (1.1% assessed as drug-related) vs. 0.8% in placebo recipients). However, patients with peanut allergy are routinely advised to treat allergic symptoms from accidental exposure to peanut immediately, prior to development of a serious reaction. Therefore, because many of these allergic reactions were treated appropriately, they did not progress to the severity of an SAE and would not be reported as SAEs. Without prompt and proper treatment (e.g. recognition of the signs and symptoms of anaphylaxis and treatment with epinephrine or other medication), the rate of SAEs could have been reported at a higher frequency. The background incidence of anaphylaxis and epinephrine use in relation to accidental food exposures in the pediatric peanut-allergic population is not well described. However, the frequencies of anaphylaxis and epinephrine use in the placebo treated recipients may provide a reasonable estimate, since these patients represent a peanut allergic pediatric population on a peanut-avoidant diet and had systematic collection of data on allergic reactions and epinephrine use.
- F: Palforzia is the first oral immunotherapy for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut in patients with a confirmed diagnosis of peanut allergy.

The REMS will consist of elements to assure safe use, including that healthcare providers who prescribe Palforzia must be specially certified, pharmacies that dispense Palforzia must be specially certified, healthcare settings that dispense Palforzia must be specially certified, Palforzia must be dispensed to patients only in certain healthcare settings, Palforzia must be dispensed to patients with evidence or other documentation of safe-use conditions, and each patient using Palforzia must be subject to certain monitoring. The REMS will also include an implementation system and a timetable for submission of assessments of the REMS.

## References:

1. Lieberman J. Increased incidence and prevalence of peanut allergy in children and adolescents in the United States. *Annals of Allergy, Asthma & Immunology*. 2018;121(5):S13

2. Savage J, Johns CB. Food allergy: epidemiology and natural history. *Immunol Allergy Clin North Am*. 2015;35(1):45–59.
3. Adkinson, N. Franklin, Bruce S. Bochner, A. Wesley Burks, W. W. Busse, S. T. Holgate, Robert F. Lemanske, Robyn E. O'Hehir, and Elliott Middleton. *Middleton's Allergy: Principles and Practice*. 8th ed. 2014 Philadelphia: Elsevier/Saunders, PA. Print.
4. Lebovidge JS, Strauch H, Kalish LA, Schneider LC. Assessment of psychological distress among children and adolescents with food allergy. *J Allergy Clin Immunol*. 2009 Dec;124(6):1282-8
5. Curtis C, Stukus D, Scherzer R. Epinephrine preparedness in pediatric patients with food allergy: an ideal time for change. *Ann Allergy Asthma Immunol*. 2014 Jun;112(6):560-2