ASSESSING ALLERGIC REACTIONS

Definitions and examples of allergic reactions of varying severity for guidance during PALFORZIA treatment based on the phase 3 PALISADE trial

INDICATION

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.

Limitation of Use: Not indicated for the emergency treatment of allergic reactions, including anaphylaxis.

IMPORTANT SAFETY INFORMATION

WARNING: ANAPHYLAXIS

- **PALFORZIA can cause anaphylaxis, which may be life threatening and can occur at any time during PALFORZIA therapy.**
- **Prescribe injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use.**
- **Do not administer PALFORZIA to patients with uncontrolled asthma.**
- **Dose modifications may be necessary following an anaphylactic reaction.**
- **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.**
- **PALFORZIA is available only through a restricted program called the PALFORZIA REMS.**

Please see additional Important Safety Information on last page.

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Peanut (*Arachis hypogaea*) Allergen Powder-dnfp

CRITERIA USED IN THE PALISADE TRIAL TO ASSESS REACTIONS INVOLVING A SINGLE ORGAN SYSTEM

In the PALISADE trial, the severity of single organ allergic reactions was assessed using the modified Consortium of Food Allergy Research (CoFAR) grading scale. The full CoFAR grading scale for allergic reactions used in the PALISADE trial is shown below. [1,2]

	 Activity Limitations	 Intervention Level	 Symptoms
MILD Grade 1	Transient or mild discomfort (<48 hrs)	No or minimal medical intervention/therapy required	Pruritus, swelling or rash, abdominal discomfort, or other transient symptoms
MODERATE Grade 2	Mild to moderate limitation in activity, some assistance may be needed	No or minimal intervention/therapy is required; hospitalization is possible	Persistent hives, wheezing without dyspnea, abdominal discomfort/ increased vomiting, or other symptoms
SEVERE Grade 3	Marked limitation in activity, some assistance usually required	Medical intervention/ therapy required; hospitalization is possible	Bronchospasm with dyspnea, severe abdominal pain, throat tightness with hoarseness, transient hypotension, other symptoms
LIFE-THREATENING Grade 4	Extreme limitation in activity; significant assistance required	Significant medical/therapy. Intervention is required; hospitalization is probable Perenteral medication(s) are usually indicated	Persistent hypotension and/or hypoxia with resultant decreased level of consciousness associated with collapse and/or incontinence or other life-threatening symptoms
DEATH Grade 5	N/A	N/A	N/A

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CRITERIA USED IN THE PALISADE TRIAL TO ASSESS THE SEVERITY OF ALLERGIC REACTIONS INVOLVING TWO OR MORE ORGAN SYSTEMS

In the PALISADE study, allergic reactions involving two or more organ systems were captured as systemic allergic reactions, a term that was used to capture all multi-organ reactions for evaluation, independent of severity.[1,2]

Systemic allergic reactions were identified using a modified version of the Sampson criteria. The severity of the allergic reactions were graded as mild, moderate or severe using the Muraro (EAACI) scale. If a systemic allergic reaction was classified as severe, it was reported as anaphylaxis in the PALISADE study.[3]

The table below shows the Muraro (EAACI) scale allergic reactions.

STAGING SYSTEM OF SEVERITY OF ANAPHYLAXIS

Stage		Defined By
I. MILD	Skin & subcutaneous tissues, GI, &/or mild respiratory	Flushing, urticaria, periorbital or facial angioedema; mild dyspnea, wheeze or upper respiratory symptoms; mild abdominal pain and/or emesis
2. MODERATE	Mild symptoms + features suggesting moderate respiratory, cardiovascular or GI symptoms	Marked dysphagia, hoarseness and/or stridor; shortness of breath, wheezing & retractions; crampy abdominal pain, recurrent vomiting and/or diarrhea; and/or mild dizziness
3. SEVERE	Hypoxia, hypotension, or neurological compromise	Cyanosis or $Sp0_2 \leq 92\%$ at any stage, hypotension, confusion, collapse, loss of consciousness; or incontinence

Criteria for Severity Grading (Muraro et al., 2007)

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IMPORTANT SAFETY INFORMATION (CONTINUED)

CONTRAINDICATIONS

PALFORZIA is contraindicated in patients with uncontrolled asthma, or with a history of eosinophilic esophagitis and other eosinophilic gastrointestinal disease.

WARNINGS AND PRECAUTIONS

Anaphylaxis

PALFORZIA can cause anaphylaxis, which may be life threatening. PALFORZIA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the PALFORZIA REMS because of the risk of anaphylaxis. Only prescribers, healthcare settings, pharmacies, and patients certified and enrolled in the REMS Program can prescribe, receive, dispense or administer PALFORZIA.

Anaphylaxis has been reported during all phases of PALFORZIA dosing, including Maintenance and in subjects who have undergone recommended Up-Dosing and dose modification procedures.

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. In addition, PALFORZIA may not be suitable for patients taking medications that can inhibit or potentiate the effects of epinephrine.

All Initial Dose Escalation doses and the first dose of each Up-Dosing level must be administered under observation in a certified health care setting.

Patients may be more likely to experience allergic reactions following PALFORZIA administration in the presence of cofactors such as exercise, hot water exposure, intercurrent illness (e.g., viral infection), or fasting. Other potential cofactors may include menstruation, sleep deprivation, nonsteroidal anti-inflammatory drug use, or uncontrolled asthma. Patients should be proactively counseled about the potential for the increased risk of anaphylaxis in the presence of these cofactors. If possible, adjust the time of dosing to avoid these cofactors. If it is not possible to avoid these cofactors, consider withholding PALFORZIA temporarily.

Asthma

Uncontrolled asthma is a risk factor for a serious outcome, including death, in anaphylaxis. Ensure patients with asthma have their asthma under control prior to initiation of PALFORZIA.

PALFORZIA should be temporarily withheld if the patient is experiencing an acute asthma exacerbation. Following resolution of the exacerbation, resumption of PALFORZIA should be undertaken cautiously. Re-evaluate patients who have recurrent asthma exacerbations and consider discontinuation of PALFORZIA.

Eosinophilic Gastrointestinal Disease

Discontinue PALFORZIA and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent gastrointestinal symptoms, including dysphagia, vomiting, nausea, gastroesophageal reflux, chest pain, or abdominal pain.

Gastrointestinal Adverse Reactions

Gastrointestinal adverse reactions were commonly reported in PALFORZIA-treated subjects, and dose modification should be considered for patients who report these reactions. For severe or persistent gastrointestinal symptoms consider a diagnosis of eosinophilic esophagitis.

ADVERSE REACTIONS

The most common adverse events reported in subjects treated with PALFORZIA (incidence ≥ 5% and at least 5% greater than placebo) are abdominal pain, vomiting, nausea, oral pruritus, oral paresthesia, throat irritation, cough, rhinorrhea, sneezing, throat tightness, wheezing, dyspnea, pruritus, urticaria, anaphylactic reaction, and ear pruritus.

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References: 1. Protocol for: The PALISADE Group of Clinical Investigators: Vickery BP, Vereda A, Casale TB, et al. *N Engl J Med.* 2018;379(21):1991-2001. doi:10.1056/NEJMoa1812856. **2.** Burks AW, Jones SM, Wood RA, et al. *N Engl J Med.* 2012;367:233-243. doi:10.1056/NEJMoa1200435. **3.** Muraro A, Roberts G, Clark A, et al. *Allergy.* 2007;62:857-871. doi:10.1111/j.1398-9995.2007.01421.x.

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