DOSE MODIFICATIONS AND MISSED DOSE MANAGEMENT

Guidance for potential dosing adjustments during Up-Dosing and Maintenance dosing*

*Dose modifications are not appropriate during Initial Dose Escalation.

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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MANAGEMENT OF CONSECUTIVE MISSED DOSES[1]

The guidelines for missed doses are to be used at the discretion of the treating physician.

CONSECUTIVE MISSED DOSES	ACTION
1 TO 2 DAYS	Patients may resume PALFORZIA at the same dose level at home.
3 OR MORE DAYS	Data are insufficient to inform resumption of PALFORZIA following 3 or more consecutive days of missed doses. Patients who miss 3 or more consecutive days of PALFORZIA should consult their healthcare providers; resumption of PALFORZIA should be done under medical supervision.

TIP: Advise patients that if a daily dose is missed, the next dose should be resumed at the usual time the following day. If patients miss 3 or more consecutive doses, they should contact your office before administering the next dose.

TIP: The healthcare provider may need to prescribe a new PALFORZIA Up-Dosing Pack and provide sample doses from the PALFORZIA Office Dose Kit for dosing until the new pack arrives.

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TEMPORARY DOSE MODIFICATION IN RESPONSE TO ALLERGIC REACTIONS[1]

Temporary dose modification of PALFORZIA may be required for patients who experience allergic reactions during Up-Dosing or Maintenance, for patients who miss doses, or for practical reasons of patient management.

Use clinical judgment to determine the best course of action, which can include maintaining the dose level for longer than 2 weeks, reducing, withholding, or discontinuing PALFORZIA doses.[1]

Allergic reactions, including gastrointestinal reactions, that are severe, recurrent, bothersome, or last longer than 90 minutes during Up-Dosing or Maintenance should be actively managed with dose modifications. Dose modifications are not appropriate during Initial Dose Escalation.

Patients may be more likely to experience allergic reactions following PALFORZIA dosing in the presence of cofactors. Temporarily withholding or decreasing PALFORZIA doses may be required in the presence of these cofactors. Use clinical judgment to determine the best course of action.

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 avoidance is not possible, consider withholding PALFORZIA temporarily.

COFACTOR EXAMPLES	
• Exercise	• Menstruation
• Hot water exposure	• Sleep deprivation
• Intercurrent illness (such as viral infection)	• Nonsteroidal anti-inflammatory drug use
• Fasting	• Uncontrolled asthma

If appropriate to re-start administering PALFORZIA in patients who experienced anaphylaxis while on PALFORZIA or who had doses withheld to avoid increased risk of anaphylaxis, consider a dose reduction and dose re-escalation based on clinical judgment.

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REINITIATION AFTER A DOSE REDUCTION IN PALISADE

Temporary dose modification of PALFORZIA may be required for patients who experience allergic reactions during Up-Dosing or Maintenance, for patients who miss doses, or for practical reasons of patient management.

Use clinical judgment to determine the best course of action, which can include maintaining the dose level for longer than 2 weeks, reducing, withholding, or discontinuing PALFORZIA doses.[1]

Reinitiating PALFORZIA: Up-Dosing after temporary dose reduction in PALISADE[2]

The following protocol from the phase 3 PALISADE trial was used during reinitiation of PALFORZIA following a reduction.

This information is provided as a reference to the PALISADE protocol only. It is up to the prescriber's discretion how to manage patients through dose modifications.

DURATION OF REDUCED DOSE	INSTRUCTIONS FOR REINITIATING DOSING AND UP-DOSING
≤4 CONSECUTIVE DAYS	• The pre-reduction dose level was resumed at home or clinic, based on clinical judgment • Up-Dosing schedule could have been kept unaltered
5-7 CONSECUTIVE DAYS	• Patient returned to clinic for observed dosing • Pre-reduction dose level was resumed or dosing was continued at the reduced dose level, based on clinical judgment • Up-Dosing was reset so patient received at least 2 weeks at the assigned dose level
8-14 CONSECUTIVE DAYS	• Patient returned to clinic for observed dosing • Dose was only to be 1 dose level above the reduced dose • If the Up-Dosing was successful, patient continued home dosing for at least 2 weeks

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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. PALFORZIA [package insert]. Brisbane, CA: Aimmune Therapeutics, Inc. **2.** The PALISADE Group of Clinical Investigators: Vickery BP, Vereda A, Casale TB, et al. Protocol for: AR101 oral immunotherapy for peanut allergy. *N Engl J Med*. 2018;379(21): 1991-2001. doi:10.1056/NEJMoa1812856.

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