**Peanut (Arachis hypogaea) allergen powder-dnfp (Palforzia™)**

**New Drug Update**

**February 2020**

<table>
<thead>
<tr>
<th>Nonproprietary Name</th>
<th>peanut (Arachis hypogaea) allergen powder-dnfp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand Name</td>
<td>Palforzia</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Aimmune</td>
</tr>
<tr>
<td>Form</td>
<td>Oral powder</td>
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</tbody>
</table>
| Strength            | Capsules: 0.5 mg, 1 mg, 10 mg, 20 mg, and 100 mg  
Sachet: 300 mg       |
| FDA Approval        | January 31, 2020                             |
| Market Availability | Available                                    |
| FDA Approval Classification | Breakthrough Therapy; Standard Review            |
| FDB Classification-Specific Therapeutic Class (HIC3) | Allergenic Extracts, Therapeutic (W7W) |

**INDICATION**

Peanut (Arachis hypogaea) allergen powder-dnfp (Palforzia) is an oral immunotherapy (OIT) indicated for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. It is approved for use in patients with a confirmed diagnosis of peanut allergy.

Treatment is intended to be given in conjunction with a peanut-avoidance diet.

The initial dose escalation may be administered to patients aged 4 through 17 years. Up-dosing and maintenance dosing may be continued in patients 4 years of age and older.

It is not indicated for the emergency treatment of allergic reactions, including anaphylaxis.

**CONTRAINDICATIONS/WARNINGS**

Peanut allergen powder-dnfp is contraindicated in patients with uncontrolled asthma or a history of eosinophilic esophagitis and other eosinophilic gastrointestinal diseases.

Boxed warnings for the risk of anaphylaxis are included in the labeling. Anaphylaxis has been reported during all phases of treatment and can be life-threatening. Patients and caregivers should be prescribed injectable epinephrine and properly trained on its use. Patients should be observed for at least 60 minutes in a healthcare setting during and after administration of the initial dose escalation and first dose of each up-dosing level. Due to the risk of anaphylaxis, peanut allergen powder-dnfp is only available through a Risk Evaluation and Mitigation Strategy (REMS) program called the Palforzia REMS. Prescribers, pharmacies, and healthcare institutions must be certified in the REMS and patients must be
enrolled. Pharmacies can only dispense peanut allergen powder-dnfp to a certified facility or to patients enrolled in the REMS (depending on treatment phase).

Treatment should not be initiated in any patient who has experienced severe anaphylaxis within the prior 60 days. The product may not be considered appropriate in patients with certain medical conditions that may diminish their ability to survive anaphylaxis, such as significantly reduced lung function, severe mast cell disorder, or cardiovascular disease (CVD), as well as for those on concurrent medications that can alter the effects of epinephrine. Patients and caregivers should be able to recognize symptoms of an allergic reaction and anaphylaxis prior to starting therapy. In addition, patients should understand that exercise, hot water exposure, intercurrent illness (e.g., viral infection), fasting, menstruation, inadequate sleep, and use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of allergic reactions. These factors should be considered regarding timing of the dose. The patients should wait to take the dose after strenuous exercise until signs of a hypermetabolic state (e.g., flushing, sweating, rapid breathing, rapid heart rate) have subsided. The patient should also avoid taking hot showers or baths immediately prior to or within 3 hours after the dose.

Other warnings include uncontrolled asthma. Peanut allergen powder-dnfp should be temporarily withheld in patients experiencing an acute asthma exacerbation and may be cautiously resumed after resolution. Consider discontinuing peanut allergen powder-dnfp therapy in those with recurrent asthma exacerbations. The product has not been evaluated in patients with severe asthma, persistently uncontrolled asthma, or patients taking long-term systemic corticosteroids.

In clinical trials, 2.7% of patients treated with peanut allergen powder-dnfp reported biopsy-confirmed eosinophilic esophagitis compared to 0% with placebo. Symptoms resolved upon discontinuing therapy. Dose adjustments should be considered in patients with gastrointestinal adverse reactions (e.g., abdominal pain, vomiting, nausea, oral pruritus, oral paresthesia).

**DRUG INTERACTIONS**

Drug interactions were not addressed in the prescribing information.

**COMMON ADVERSE EFFECTS**

In clinical trials, the highest incidence of adverse effects with peanut allergen powder-dnfp were reported during the up-dosing period. The most commonly reported adverse events were (incidence ≥ 10% and ≥ 5 percentage points over placebo): abdominal pain (67.1%), vomiting (36.5%), nausea (32.3%), oral pruritus (31.2%), oral paresthesia (13.6%), throat irritation (40.3%), cough (31.9%), rhinorrhea (20.9%), sneezing (20.2%), throat tightness (14.1%), wheezing (12.3%), pruritus (32.5%), and urticaria (28.4%).

Anaphylactic reaction occurred in 9.1% of patients treated with peanut allergen powder-dnfp versus 3.5% in patients who received placebo. A total of 21.9% of patients taking peanut allergen powder-dnfp discontinued therapy for any reason compared to 6.5% of patients taking placebo. Adverse effects resulted in treatment discontinuation in 9.2% of patients during the initial dose escalation and up-dosing periods combined and in 1% during the maintenance phase. Median time onset of adverse effect symptoms was 4 minutes and the median time to resolution was 37 minutes.
SPECIAL POPULATIONS

Pregnancy
There are no data for the use of peanut allergen powder-dnfp in pregnant women to inform of maternal or fetal risks. A pregnancy exposure registry was created to monitor outcomes of peanut allergen powder-dnfp in pregnant women.

Pediatrics
Safety and efficacy in patients < 4 years of age have not been established.

DOSAGES
Contents of the capsules or sachet should be mixed with semisolid food (e.g. applesauce, yogurt, pudding) and mixed well. The entire volume of the mixture should be consumed promptly. Patients should wash hands immediately after handling the capsules/sachets. Capsules should not be swallowed whole. For oral administration only.

Peanut allergen powder-dnfp treatment is administered in 3 sequential phases: initial dose escalation, up-dosing, and maintenance. The product is packaged to provide total capsules/sachets specific for each separate phase.

Each dose should be consumed with a meal, at approximately the same time each day, preferably in the evening.

Initial Dose Escalation (single day dose escalation):

- Each dose level is administered in a sequential order on a single day in a healthcare setting that is enrolled in the REMS with the ability to manage severe allergic reactions, including anaphylaxis.
- Patients are observed for 20 to 30 minutes between each dose level and for at least 60 minutes after the last dose. Discontinue therapy if medical intervention is required (e.g. epinephrine).
- Patients who tolerate at least a 3 mg single dose (Level D) must return to the healthcare facility to initiate the up-dosing phase, if possible, as soon as the next day. If up-dosing cannot be started within 4 days, then the initial dose escalation phase must be repeated.
- Do not alter the dosing schedule as described in the table below.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Total Dose</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.5 mg</td>
<td>One 0.5 mg capsule</td>
</tr>
<tr>
<td>B</td>
<td>1 mg</td>
<td>One 1 mg capsule</td>
</tr>
<tr>
<td>C</td>
<td>1.5 mg</td>
<td>One 0.5 mg capsule + one 1 mg capsule</td>
</tr>
<tr>
<td>D</td>
<td>3 mg</td>
<td>Three 1 mg capsules</td>
</tr>
<tr>
<td>E</td>
<td>6 mg</td>
<td>Six 1 mg capsules</td>
</tr>
</tbody>
</table>
Up-dosing:
- The initial dose escalation phase should be completed before starting the up-dosing phase.
- Dose levels are given sequentially, each for a duration of 2 weeks.
- The first dose of each level is administered in a healthcare setting enrolled in the REMS.
- Patients are observed for at least 60 minutes. If tolerated, the subsequent doses of that level can be continued at home.
- Consider dose modification or discontinuation in patients who do not tolerate the regimen as described in the table below.

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Total Daily Dose</th>
<th>Configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 mg</td>
<td>Three 1 mg capsules</td>
</tr>
<tr>
<td>2</td>
<td>6 mg</td>
<td>Six 1 mg capsules</td>
</tr>
<tr>
<td>3</td>
<td>12 mg</td>
<td>Two 1 mg capsules + one 10 mg capsule</td>
</tr>
<tr>
<td>4</td>
<td>20 mg</td>
<td>One 20 mg capsule</td>
</tr>
<tr>
<td>5</td>
<td>40 mg</td>
<td>Two 20 mg capsules</td>
</tr>
<tr>
<td>6</td>
<td>80 mg</td>
<td>Four 20 mg capsules</td>
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<tr>
<td>7</td>
<td>120 mg</td>
<td>One 20 mg capsule + one 100 mg capsule</td>
</tr>
<tr>
<td>8</td>
<td>160 mg</td>
<td>Three 20 mg capsules + one 100 mg capsule</td>
</tr>
<tr>
<td>9</td>
<td>200 mg</td>
<td>Two 100 mg capsules</td>
</tr>
<tr>
<td>10</td>
<td>240 mg</td>
<td>Two 20 mg capsules + two 100 mg capsules</td>
</tr>
<tr>
<td>11</td>
<td>300 mg</td>
<td>One 300 mg sachet</td>
</tr>
</tbody>
</table>

Maintenance phase:
- All levels of the up-dosing phase should be completed prior to starting the maintenance phase.
- Maintenance dosage is 300 mg once daily.
- Daily dosing is needed to maintain therapeutic effect.
- Patient should be contacted on a regular basis by a clinician to assess for treatment-related adverse reactions.

Dose modifications/discontinuation:
- Dose adjustments may be required during the up-dosing and maintenance phases if patients experience allergic reactions, miss a dose, or for practical reasons. Actions include maintaining the dose level for greater than 2 weeks, as well as reducing, withholding, or discontinuing the dose.
- If 1 to 2 consecutive doses are missed, therapy can resume at the same dose level. Resuming therapy after 3 or more doses should be done under medical supervision.
- Discontinue treatment if the patient cannot tolerate a 3 mg dose (including during the initial dose escalation), is unable to comply with daily dosing, develops suspected eosinophilic esophagitis, or experiences recurrent asthma exacerbations.
CLINICAL TRIALS2,3,4

A literature search was performed using “AR101” and “peanut allergy.”

The phase 3 PALISADE trial enrolled 555 peanut-allergic patients ages 4 to 55 years (n=499; ages 4 to 17 years). Most patients had a history of peanut anaphylaxis (72%), asthma (53%), or multiple food allergies (66%). Inclusion criteria were:

- Clinical history of allergy to peanuts or peanut-containing foods;
- Serum immunoglobulin E (IgE) to peanut ≥ 0.35 kUA/L (kilos of allergen-specific units per liter, determined by UniCAP™ within the past 12 months) and/or a skin prick test (SPT) to peanut with a mean wheal diameter ≥ 3 mm compared to control;
- Patient experienced dose-limiting symptoms at or before the 100 mg challenge dose of peanut protein (measured as 200 mg of peanut flour) on screening conducted in accordance with PRACTALL (PRACTical issues in ALLergology Joint United States/European Union Initiative) guidelines.

Key exclusion criteria were:

- History of CVD, including uncontrolled or inadequately controlled hypertension;
- History of severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days;
- History of chronic disease (other than asthma, atopic dermatitis, or allergic rhinitis) that is or is at significant risk of becoming unstable or requiring a change in chronic therapeutic regimen;
- History of eosinophilic esophagitis, other eosinophilic gastrointestinal (GI) disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia, or recurrent GI symptoms of undiagnosed etiology;
- History of a mast cell disorder, including mastocytosis, urticarial pigmentosa, and hereditary or idiopathic angioedema.

Eligible patients were randomized 3:1 to peanut (Arachis hypogaea) allergen powder-dnfp or matching placebo. The treatment regimen comprised a 1-day, supervised, initial dose escalation phase (from 0.5 mg to 6 mg); an increasing-dose phase, during which the dose was increased gradually every 2 weeks from 3 mg to 300 mg; and a 24-week maintenance phase with a daily dose of 300 mg. Patients were to continue a strict peanut-avoidance diet and to carry injectable epinephrine. At study screening, the median maximum dose of peanut protein tolerated during a food challenge was 10 mg. At the end-of-trial visit, patients were subjected to an exit double-blind, placebo-controlled food challenge (DBPCFC).

The primary efficacy endpoint was the proportion of patients 4 to 17 years of age who were considered to have a response to treatment, which was defined as the ability to tolerate a single oral dose of at least 600 mg of peanut protein (equivalent to ≥ 2 peanuts) during the exit food challenge, with no dose-limiting symptoms, as judged by the investigator.

After 6 months of maintenance treatment, 67.2% of patients ages 4 to 17 years who received active treatment were able to consume ≥ 600 mg of peanut protein (equivalent to ≥ 2 peanuts) with no reaction or only a mild reaction compared to 4% of patients treated with placebo (63.2% difference; 95% confidence interval [CI], 53 to 73.3; p<0.001). Among patients aged 4 to 17 years, during the treatment period (excluding the exit challenge), 98.7% and 95.2% of patients in the active-drug and placebo groups, respectively, experienced an adverse event, and 4.3% and 0.8%, respectively, were severe events. During the treatment period, 14.2% of patients in the active-drug group (including one grade 3 anaphylaxis event) and 3.2% in the placebo group had a systemic allergic reaction. The remainder of the events in
the active-drug group were mild (6.2% of patients) or moderate (7.8% of patients) in severity. In addition, during the treatment period, 14% of patients in the active-drug group received epinephrine compared to 6.5% in the placebo group; however, nearly 94% of the events in the active-drug group for which epinephrine was given were of grade 1 or 2 severity.

In the exit food challenge, 10% of patients in the active-drug group received rescue epinephrine, and the median dose at which it was given was 1,000 mg of peanut protein, compared to 53% of patients in the placebo arm were given epinephrine at a median dose of 100 mg.

Most treatment-related adverse events occurred during the up-dosing phase and were GI in nature (abdominal pain, vomiting, nausea), or involved pruritus (including oral) or throat irritation/cough. Approximately 79% of patients in the active-drug group completed the study; 11.6% withdrew during the intervention period due to adverse effects compared to 2.4% in the placebo group. No significant change in peripheral-blood eosinophil levels were reported in either study group.

Efficacy was not shown in participants ≥ 18 years of age. The response rate of ability to tolerate 600 mg peanut protein was 41.5% for the active-drug group compared to 14.3% in the placebo group (difference was not statistically significant).

**OTHER DRUGS USED FOR CONDITION**

There is currently no treatment for peanut allergy approved by the United States (US) Food and Drug Administration (FDA) with the exception of peanut (*Arachis hypogaea*) allergen powder-dnfp (Palforzia). The main approach to managing food allergy is to avoid the offending allergen. Notably, the American Academy of Pediatrics (AAP) and the National Institute of Allergy and Infectious Diseases (NIAID) support early introduction of peanut protein to prevent peanut allergy in infants who are at increased risk of developing peanut allergy (e.g., history of severe eczema and/or egg allergy).

While non-approved oral immunotherapy (OIT) for peanut allergy is utilized to desensitize patients to peanut protein, it lacks standardization.

**PLACE IN THERAPY**

Peanut allergy is a public health concern with a significant burden on patients and caregivers. Approximately 2.5% of children in the US suffer from peanut allergy and this figure is rising. Furthermore, only a small number of children outgrow their peanut allergy. Reaction to peanut exposure varies from mild skin and/or gastrointestinal symptoms to severe angioedema and anaphylaxis. When accidental peanut exposure occurs (estimated annual incidence up to 10% to 20%), antihistamines can manage mild to moderate reactions, but patients must carry an epinephrine auto-injector to treat severe reactions.

Peanut (*Arachis hypogaea*) allergen powder-dnfp (Palforzia) is a biologic oral immunotherapy consisting of 12% defatted peanut flour with a standardized allergen profile. The dose is titrated under the supervision of an healthcare provider to a target oral maintenance dose of 300 mg daily. Peanut allergen powder-dnfp is not a cure for peanut allergy and desensitization with this product is intended to continue indefinitely. No adequate trials have been conducted demonstrating sustained tolerance after stopping peanut allergen consumption. A major concern with immunotherapy is loss of allergen tolerance if regular consumption is stopped.

While patients must still continue to avoid dietary peanuts, with the exception of the prescribed daily consumption, and carry injectable epinephrine, peanut allergen powder-dnfp provides a consistent dose
of peanut allergen to increase a patient’s tolerance to accidental peanut exposure and reduce the risk of serious allergic reactions. In clinical trials, the most common adverse effects were gastrointestinal in nature. In the PALISADE clinical trial, two-thirds of patients ages 4 to 17 years were able to tolerate a dose of 600 mg of peanut protein after 6 months of treatment. While 10% of patients required epinephrine rescue upon peanut allergen rechallenge, significantly fewer patients who received peanut allergen powder-dnfp required rescue and at a much higher peanut allergen dose compared to patients who received placebo. Efficacy of peanut allergen powder-dnfp was not shown in participants ≥ 18 years of age.

The Institute for Clinical and Economic Review (ICER) published their final evidence report on therapy for peanut allergy in July 2019 which discusses peanut allergen powder-dnfp. ICER states that while peanut allergen powder-dnfp led to desensitization to the peanut allergen, data have not been reported regarding impact on quality of life, although the product has the potential to do so. A number of other sources note a lack of a standard definition for desensitization, which can pose a challenge when evaluating and comparing safety and effectiveness of peanut allergy products. ICER concluded that evidence was inadequate to demonstrate a superior net health benefit of peanut allergen powder-dnfp (Palforzia) compared to strict peanut avoidance. In addition, studies of unregulated OIT have also reported successful desensitization (range, 21% to 49% of participants). Patients/caregivers and clinicians may be more comfortable using a standardized treatment protocol, such as peanut allergen powder-dnfp over unregulated OIT. Moreover, the sustained unresponsiveness to peanut allergens with long-term use of peanut allergen powder-dnfp is has not been proven.

Peanut allergen powder-dnfp (Palforzia) is only available through a restricted REMS program. Patients as well as prescribers, pharmacies, and healthcare institutions involved in treatment must be enrolled.

Ongoing trials are evaluating peanut allergen powder-dnfp (Palforzia) in patients 1 to 3 years of age and its long-term (3 years) safety and tolerability profile. DBV Technologies has submitted their transdermal therapy for peanut allergy Viaskin peanut to the FDA for approval. The FDA decision on Viaskin peanut is anticipated by August 5, 2020.
# SUGGESTED UTILIZATION MANAGEMENT

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<thead>
<tr>
<th>Anticipated Therapeutic Class Review (TCR) Placement</th>
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<tr>
<td><strong>Clinical Edit</strong></td>
<td><strong>Initial Approval Criteria</strong></td>
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</table>

- Patient must be 4 to 17 years of age; **AND**
- Patient must have a documented clinical history of allergy to peanuts or peanut-containing foods; **AND**
- Confirmed diagnosis of peanut allergy based on:
  - Serum immunoglobulin E (IgE) to **peanut** ≥ 14 kUA/L (kilos of allergen-specific units per liter) within the past 12 months; **OR**
  - Skin prick test (SPT) to **peanut** with a mean wheal diameter of ≥ 8 mm compared to control; **OR**
  - Clinical history of systemic reaction to peanut within the last 2 years with evidence of sensitization to peanut (serum IgE ≥ 0.35 and/or peanut SPT ≥ 3 mm); **OR**
  - *Documented* reaction to peanut upon supervised oral food challenge at a dose of ≤ 100 mg peanut protein (≤ 200 mg peanut flour); **AND**
- Patient does **NOT** have any of the following:
  - Severe asthma (e.g., currently treated with high-dose inhaled corticosteroid/long-acting beta-agonist therapy; has forced expiratory volume in 1 second [FEV₁] < 60% of predicted); **OR**
  - Persistently uncontrolled mild to moderate asthma (defined as FEV₁ < 80% predicted); **OR**
  - Three to four of the following symptoms: daytime asthma symptoms > twice/week, and nighttime awakening due to asthma symptoms, asthma reliever medication use > twice/week [excluding reliever taken for exercise], or any activity limitation due to asthma); **AND**
- Patient has **NOT** received systemic corticosteroid therapy (oral, intramuscular, intravenous) for the treatment of asthma in any of the following manners:
  - Daily systemic corticosteroid for > 1 month during the past year; **OR**
  - More than 2 burst systemic corticosteroid courses in the past year with ≥ 1 week in duration; **OR**
  - Burst systemic corticosteroid course within 3 months prior to starting Palforzia; **AND**
- Patient has **NOT** been hospitalized for asthma within 1 year prior to starting Palforzia; **AND**
  - Patient has **NOT** had emergency department (ED) visit for an asthma exacerbation within 6 months prior to starting Palforzia; **AND**
- Patient does **NOT** have a history of eosinophilic esophagitis, and/or other eosinophilic gastrointestinal diseases; **AND**
- Patient does **NOT** have uncontrolled atopic dermatitis; **AND**
• Patient does NOT have a medical condition that inhibits their ability to survive anaphylaxis, such as significantly reduced lung function, severe mast cell disorder, or cardiovascular disease; **AND**
• Patient is NOT currently taking medications that can alter the effects of epinephrine (e.g., beta-blockers [oral], angiotensin-converting enzyme (ACE) inhibitor; angiotensin receptor blocker [ARB], calcium channel blocker [CCB], alpha-adrenergic blocker, ergot alkaloid); **AND**
• Patient has NOT experienced severe anaphylaxis resulting in hypotensive shock, use of > 2 doses of epinephrine, and/or intubation within the prior 60 days; **AND**
• Palforzia is being requested by or in consultation with a specialist (Allergy and Immunology specialists)
• Patient has been prescribed and/or has a refill history of epinephrine auto-injector; **AND**
• Prescriber attestation for the following:
  – Patient/caregiver understand how to use injectable epinephrine; **AND**
  – Patient/caregiver must be able to recognize the signs and symptoms of a serious allergic reaction and anaphylaxis; **AND**
  – Patient/caregiver understands the importance of continual daily dosing of Palforzia to sustain desensitization and will adhere to a daily dosing regimen, including maintenance phase, of Palforzia as prescribed; **AND**
  – Patient/caregiver will temporarily withhold Palforzia and contact the prescriber if the patient experiences an acute asthma exacerbation; **AND**
  – Patient/caregiver understands dose timing considerations (e.g., strenuous exercise, hot shower/bath); **AND**
• Palforzia will be initiated at a REMS-certified healthcare facility; the initial dose escalation phase and the first dose of each of the 11 up-dosing phases will be given at a REMS-certified healthcare facility; **AND**
• Patient/caregiver will adhere to the complex up-dosing schedule that requires frequent visits to the administering healthcare facility

**Renewal Criteria**

• Patient must continue to meet the above initial criteria; **AND**
• Patient must continue to tolerate the prescribed daily doses of Palforzia; **AND**
• Patient has not experienced recurrent asthma exacerbations; **AND**
• Patient has not have experienced any treatment-restricting adverse effects (e.g., repeated systemic allergic reaction and/or severe anaphylaxis)

*Note: patients ≥ 18 years of age who met the initial approval criteria may continue maintenance treatment upon renewal*
**Quantity Limit**

| Initial Dose Escalation kit: 1 kit total (contains 5 doses)  
| Up-Dosing kit: 11 kits (1 kit per each dose level);  
| - Temporary dose modifications may be encountered during the Up-Dosing phase, thereby extending the duration of any dosing level beyond 2 weeks). This may result in the need for > 11 kits  
| Maintenance: 30 sachets (300 mg each)/30 days |

**Duration of Approval**

| Initial: 8 months  
| Renewal: 1 year |

**Drug to Disease Hard Edit**

- Uncontrolled asthma;  
- History of eosinophilic esophagitis and/or other eosinophilic gastrointestinal diseases;  
- Prior history of intubation during anaphylactic reaction or asthma exacerbation

**REFERENCES**