Subject: Palforzia [Peanut (Arachis hypogaea) Allergen Powder-dnfp]  | Original Effective Date: Q2 2020
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Policy Number: MCP-360  | Revision Date(s):
P&T Approval Date: Q2 2020

**Disclaimer**

This Molina Clinical Policy (MCP) is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this MCP document and provide the directive for all Medicare members.

**Summary of Evidence/Position**

This policy addresses Palforzia [Peanut (Arachis hypogaea) Allergen Powder-dnfp] for the treatment of peanut allergy in children when appropriate criteria are met.

The intent of this policy, Palforzia, is to ensure appropriate selection of patients for therapy based on product labeling, clinical studies, nationally recognized authoritative references and current peer-reviewed scientific literature. The information outlined in the Molina Clinical Policy includes but is not limited to a review of evidence based information obtained from the following sources Evaluation of New and Existing Technologies (UM 10). This policy is intended to address coverage criteria that are appropriate for the majority of individuals/members with a particular disease, illness, or condition. Each member's unique clinical circumstances may warrant individual consideration, based on review of applicable medical records.

Molina Healthcare reserves the right to update this policy and revise coverage criteria to include or omit any off-label condition(s) as necessary based on medical literature and clinical studies that may become available.

**Peanut allergy**

- An immunoglobulin E (IgE)-mediated allergic response to ingested peanut protein causing severe reactions, including urticaria, hypotension, anaphylaxis, cardiac arrest and is the leading cause of anaphylaxis and death due to food allergy
- Diagnosis remains a detailed history coupled with skin prick tests and/or specific IgE to peanut: both skin prick tests and specific IgE to peanut are highly sensitive (95%) but specificity is poor (around 60%).
  - A negative test is useful for excluding peanut allergy, whereas a high positive result coupled with a positive history has a high likelihood ratio for peanut allergy. However, for those with intermediate results, further specialized tests such as food challenges may be required to differentiate between asymptptomatically sensitized and truly allergic patients. Food challenges are time-consuming, labor-intensive and potentially hazardous, requiring expertise narrowed to certain centers.
- A growing public health problem that affects an estimated 2% of children in the U.S. (Togias et al., 2017); often presents in early childhood, and may persist or develop in adulthood
  - There are no FDA-approved curative treatments and spontaneous resolutions to peanut allergies are rare. Historically, the standard of care for peanut allergies consists of strict avoidance along with a prescription for an epinephrine auto-injector as first-line for anaphylaxis to treat anaphylaxis after accidental allergen exposure.
However, the National Institute of Allergy and Infectious Diseases (NIAID) completely reversed their recommendations for children at risk of peanut allergy in 2017 after the Learning Early About Peanut allergy (LEAP) trial showed that children at high risk for having peanut allergy were less likely to develop an allergy if they were exposed to peanuts within their first 12 months of life. Of the infants at high risk of developing a peanut allergy, only 1.9 percent who were introduced to peanuts early on developed a peanut allergy by age 5 compared to 13.7 percent who avoided peanuts.

**Palforzia**
The first oral immunotherapy (OIT) approved for peanut allergy
- With OIT, specific allergenic proteins are ingested initially in very small quantities, followed by incrementally increasing amounts, resulting in the ability to mitigate allergic reactions to the allergen over time
- A powder manufactured from defatted peanut flour; supplied as a capsule or sachet to empty into onto a few spoonfuls of refrigerated or room temperature semisolid food

**Efficacy**
The FDA approval of Palforzia was primarily based on PALISADE (Peanut ALlergy oral Immunotherapy Study of AR101 for DEsensitization in children and adults) was a phase III, randomized, double-blinded, placebo-controlled study, enrolling more than 555 eligible participants aged 7 to 17 years with peanut sensitivities. At screening, all the participants had an allergic reaction, with dose-limiting symptoms, to no more than 100 mg of peanut protein (equivalent to approximately one third of a peanut kernel).
- Dose escalation period of approximately 22 weeks to reach a maintenance dose of 300 mg per day of AR101 or placebo, then continued with daily maintenance at 300 mg per day of AR101 or placebo for approximately six months.
- At the end of the study period (total duration of the trial was approximately 12 months) patients underwent an exit DBPCFC, which tested consecutive doses of 3, 10, 30, 100, 300, 600 and 1,000 mg of peanut protein, given 20 to 30 minutes apart, as tolerated with no more than mild symptoms.
- The primary outcome was the proportion of participants 4 to 17 years of age who could ingest 600mg or more of peanut protein (twice the daily maintenance dose of Palforzia and equivalent to 2 peanut kernels) with no more than mild allergic symptoms in an exit food challenge at the end of the 6-month maintenance period (DBPCFC after approximately one-year follow-up).
- Of the children on active treatment (300 mg/day of peanut protein), 77% tolerated the 300 mg dose, and 67% (250 of 372) were able to ingest ≥ 600 mg of peanut protein (equivalent to approximately two peanut kernels) with no more than mild symptoms at the exit peanut challenge compared with 4% in the placebo group.
- Only 10% of participants ages 4-17 who received Palforzia needed to use rescue epinephrine for their symptoms during the food challenge at the end of the maintenance period, compared to 53% who received a placebo. (PALISADE; Vickery et al.)

**Safety Analysis and Other Considerations of OIT**
- In the PALISADE Phase III oral immunotherapy study:
  - Adverse events led to the withdrawal of 12.4% of the active group versus only 1.6% of the placebo group (Vickery et al. PALISADE 2018)
  - 34.7% of the participants had events with a highest severity of mild, and 59.7% had events with a highest severity of moderate, as compared with 50.0% and 44.4%, respectively, in the placebo group. Out of these groups, 5.6% of patients in the Palforzia group reported serious adverse events compared to 1.6% of patients in the placebo group.
  - Most notably, 14.2% of patients in the Palforzia group experienced serious allergic events compared to 3.2% of patients in the placebo group.
According to a large meta-analysis of 12 clinical trials (n=1041, median age of participants 8.7 years) published by Chu et al., peanut OIT increased the likelihood of passing an in-clinic food challenge compared with an elimination diet alone, 40% versus 3%. However, it is important to note that individuals on OIT had three times the risk for having anaphylaxis during the maintenance phase (22% versus 7%), were between two and three times more likely to use epinephrine (8.2% versus 3.7%), and increased the frequency of vomiting and other gastrointestinal symptoms (33% versus 19%), and increased other adverse events. OIT resulted in patients twice as likely to have a serious, life-threatening reaction compared to patients not on OIT. The meta-analysis concluded that there were no reported clinical benefits such as a reduction in allergic reactions due to accidental peanut exposure or a reduction in anaphylaxis. There were no significant differences in quality of life between the OIT and placebo groups. (Chu et al. PACE 2019).

NOTE: The trials included in the meta-analysis varied with respect to the OIT formulation and dosing protocol used. However, in subgroup analysis, the findings were consistent irrespective of OIT protocol and whether or not a proprietary formulation or readily available peanut flour was used.

A randomized long-term trial of peanut OIT in adults and children found that over 80% of patients in the high-dose OIT group were desensitized at two years, compared with 4 percent in the placebo group (Feuille 2018), However, one-year SU was achieved in only 37% of those switched from high- to low-dose therapy and in only 13% of those who discontinued therapy. These results suggest that ongoing high-dose peanut exposure is necessary to maintain the protective effect of peanut OIT (Nowak-Węgrzyn; UTD 2020)

Efficacy in clinical trials has typically been defined by induction of a desensitized state. “Desensitization” refers to the improvement in food challenge outcomes after therapy and relies on ongoing exposure to the allergen. It is important to note that because efficacy has been measured using oral food challenges in trials, it is not yet definitively known whether desensitization can protect patients from real-world accidental exposures (e.g. prevent hospitalization or death).

- It is challenging to fully evaluate the impact of OIT therapies for peanut allergy since there is currently no accepted standard definition for desensitization (ICER 2019). Desensitization is a surrogate outcome for the clinically meaningful outcomes of a decrease in allergic reactions to accidental exposure to peanuts, reduction in epinephrine use and improvement in quality of life (QOL); however studies yet to demonstrate that desensitization to peanut protein improves these outcomes. Primary outcome differed across all of the trials. ICER also noted the primary benefit of desensitization to peanuts is likely to be the improvements in QOL for both the patient and caregivers; however there is a lack of Phase 3 trials with placebo-controlled assessments for QOL outcomes published to date (ICER 2019).

- The net health benefits of Palforzia will be determined by changes in QOL and reductions in reactions to accidental exposure to peanuts, neither of which has been demonstrated.

Sustained unresponsiveness has not been adequately studied to provide definitive data regarding the magnitude or durability of the long-term benefits of this intervention. While there is optimism that a subset of peanut allergic patients may develop sustained unresponsiveness, the current assumption is that patients will remain on these therapies indefinitely. Long-term adherence to indefinite therapy may become a significant issue if patients are not continuously adherent, and consequently, may no longer be desensitized resulting in a serious allergic reaction to the therapy itself.

Specificity of Peanut OIT: Peanut OIT provides a measure of protection against peanut protein, however does not affect reactivity in co-existing allergies such as tree nut allergies.
**FDA INDICATIONS**

**Peanut allergy:** Oral immunotherapy for mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut in patients with a confirmed diagnosis of peanut allergy. Initial dose escalation may be administered to patients 4 to 17 years of age. Up-dosing and maintenance may be continued in patients \( \geq 4 \) years of age. Peanut allergen powder 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

*Available as:* Sprinkle Capsule, Oral: 0.5 mg, 1 mg, 10 mg, 20 mg, 100 mg; Sprinkle Packet, Oral: 300 mg

*Approved by the FDA:* January 31, 2020

**Boxed Warning** Anaphylaxis: Peanut allergen powder can cause anaphylaxis, which may be life-threatening and can occur at any time during 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 peanut allergen powder 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. Because of the risk of anaphylaxis, peanut allergen powder is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS).

**REMS program** Palforzia will only be available through specially certified healthcare providers, health care settings, and pharmacies to patients who are enrolled in the Palforzia REMS program. REMS requirements include:
- The prescribing physician and patient must be enrolled in the REMS prior to initiation of treatment.
- The initial dose escalation and the first dose of each up-dosing level must be administered in a certified healthcare setting.
- Epinephrine must always be immediately available to patients.
- Pharmacies/distributors must be certified with the REMS and dispense Palforzia only to certified healthcare settings or to patients who are enrolled in the REMS.

**CLASSIFICATION:** Allergen-Specific Immunotherapy

**COVERAGE CRITERIA FOR INITIAL AUTHORIZATION**

Palforzia [Peanut (Arachis hypogaea) Allergen Powder-dnfp] may be authorized for members who meet ALL of the following criteria [ALL]

1. **Prescriber specialty [ALL]**
   - Board-certified allergist or immunologist with experience in OIT therapy and administration in health care setting, with the ability to manage potentially severe allergic reactions, including anaphylaxis
   - AND
   - Both the Prescriber and the health care setting in which Palforzia will be administered is certified through the REMS program
2. Diagnosis/Indication [ALL]

☐ Clinical history or medical records of an allergic reaction to peanut includes the following documentation [ALL]

☐ Signs and symptoms of a significant systemic allergic reaction that occurred within a short period following a known ingestion of peanut or peanut-containing food. Signs and symptoms of a significant systemic allergic reaction include hives, swelling, wheezing, hypotension, and gastrointestinal symptoms

AND

☐ Prior claim or pharmacy record of a fill of epinephrine autoinjector (e.g. EpiPen, EpiPen Jr., Auvi-Q, and generic epinephrine auto-injectors) OR prescriber attestation that member was prescribed epinephrine auto-injector due to the confirmed peanut allergy

AND

☐ Member meets ONE (1) of the following: [1 OR 2]

1) For members who have NOT had a clinician-supervised food challenge: Peanut allergy is confirmed by the BOTH the following [BOTH]

☐ Positive skin prick test to peanut ≥8 mm compared to control [unless skin testing is contraindicated]^RAMSES

AND

☐ Serum IgE to peanut ≥14 kUA/L^RAMSES

OR

2) For members who had a positive clinician-supervised oral food challenge, peanut allergy is confirmed by ONE (1) of the following: [ONE]

☐ Positive skin prick test (SPT) to peanut ≥3 mm compared to control^PALISADE BSACI Guidelines, Allergy/Immunology Review 2020

OR

☐ Serum IgE to peanut ≥ 0.35 kUA/L (kilos of allergen-specific units per liter) within the past 12 months^PALISADE

AND

☐ Number of physician office/ER visits/hospitalizations due to peanut allergy. Prescriber submit documentation should include all visits related to anaphylaxis, allergic reaction(s) or significant symptoms.

MOLINA REVIEWER: Document baseline number in member’s authorization since continuation of therapy requests require follow-up documentation as evidence of positive benefit from therapy.

3. Age/Gender/Other restrictions [ALL]

☐ Member is 4 to 17 years of age

OR

Member ≥ 18 years of age AND started Palforzia therapy at 17 years of age or younger (applicable for members new to Molina and requesting continuation of therapy)

† Safety and effectiveness have not been established in persons younger than 4 years of age.

† To date, there is insufficient evidence to support the initiation of Palforzia therapy past the age of 17 years. Studies in adults are on-going.
4. Step/Conservative Therapy/Other condition Requirements [ALL]

- Member will use in conjunction with a peanut-avoidant diet; **AND**

**AND**
- Member has a current prescription for epinephrine and access to an epinephrine autoinjector while using Palforzia. **MOLINA REVIEWER:** Review profile for epinephrine claim or enter an authorization if applicable
  - In the PALISADE trial, epinephrine use for any reason was reported in 10.4% of Palforzia-treated subjects compared with 4.8% of placebo-treated subjects during Initial Dose Escalation and Up-Dosing combined, and in 7.7% of Palforzia-treated subjects compared with 3.4% of placebo-treated subjects during Maintenance dosing.

**AND**
- Member has NOT experienced severe or life-threatening episode of anaphylaxis or anaphylactic shock in the last 60 days

**AND**
- NOT prescribed for use in combination other peanut desensitization therapy. Documentation required.

**AND**
- Prescriber has discussed the adverse effect profile, risks and burdens of peanut oral immunotherapy (PN OIT) with member and guardian, including the long-term duration and adherence to therapy

**NOTE:** Accurate information on the anticipated effects of OIT should be provided to patient/guardian-- OIT does not reduce the risk of anaphylaxis and in fact, it increases the risk; furthermore, based upon the available data, OIT does not appear to improve quality of life (QOL) (Nowak-Węgrzyn; UTD 2020)

5. Contraindications/Exclusions/Discontinuations to Palforzia therapy

Authorization will not be granted if ANY of the following conditions apply [ANY]

- Non-FDA approved indications
- Concurrent use with other peanut desensitization therapy
- History of severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days
- Severe, unstable or uncontrolled 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.*
- History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension
- History of eosinophilic esophagitis and other eosinophilic GI disease
- 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 (EoE), other eosinophilic gastrointestinal disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia or recurrent gastrointestinal symptoms of undiagnosed etiology
- History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism (e.g., cold urticaria, cholinergic urticaria), and hereditary or idiopathic angioedema
- Pregnancy
  - *Accidental exposure to peanuts in a peanut allergic woman may cause anaphylaxis, which may then decrease maternal BP and placental perfusion. Anaphylaxis may also occur following exposure to peanut allergen powder.*
  - *Pregnant women were excluded from initial studies of peanut allergen powder as oral immunotherapy (PALISADE Group [Vickery 2018]). In general, immunotherapy should not be initiated during pregnancy (Pitsios 2019). Data collection to monitor pregnancy and infant outcomes following exposure to peanut allergen powder is ongoing. Health care providers are encouraged to enroll females exposed to peanut allergen powder during pregnancy in the pregnancy registry (1-833-246-2566).*
6. Labs/Reports/Documentation required [ALL]
All documentation for determination of medical necessity must be submitted for review. Prescriber to submit documentation as indicated in the criteria above, including but not limited to chart notes, applicable lab values and/or tests, adverse outcomes, treatment failures, or any other additional clinical information or clinical notes from the member’s medical records supporting the diagnosis. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP are included.

NOTE: Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

REAUTHORIZATION / CONTINUATION OF THERAPY

Palforzia [Peanut (Arachis hypogaea) Allergen Powder-dnfp] may be authorized for continuation of therapy if meet ALL of the following criteria are met: [ALL]

1. Initial Coverage Criteria [ALL]
   - Member currently meets ALL initial coverage criteria
   
   AND
   - Member ≥ 18 years of age AND has been previously started on therapy with Palforzia prior to becoming 18 years of age and have been on continuous desensitization therapy. Prescriber attestation of continuous therapy and member’s compliance is required. NOTE: There must not be gaps in therapy

   AND
   - Subsequent authorizations will require the Member re-assessment for this condition to determine if continuation of treatment with requested medication is medically necessary. Clinical documentation indicating must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Compliance
   - Continuous adherence to therapy as verified by:
     - Member’s claim history (Molina Reviewer: Review member’s prescription claims history for compliance): Any indication of compliance or adherence issues should be discussed with discussed with Prescriber and Medical Director for a treatment plan or discontinuation of treatment
       - There is significant uncertainty about the magnitude or durability of the long-term benefits of this intervention. While there is optimism that a subset of peanut allergic patients may develop sustained unresponsiveness, the current assumption is that patients will remain on these therapies indefinitely. Long-term adherence to indefinite therapy may become a significant issue if patients are not continuously adherent, and consequently, may no longer be desensitized resulting in a serious allergic reaction to the therapy itself.
     - Documentation of physician office visits for administration is consistent with FDA-approved labeling schedule
3. Labs/Reports/Documentation required [ALL]

☐ Palforzia maintenance therapy may be authorized when therapy has demonstrated efficacy as evidenced by an improvement in member’s condition after therapy and DOCUMENTED by ALL of the following: [ALL]

дра Number of physician office/ER visits/hospitalizations due to peanut allergy, not including visits for dosing, since the previous authorization visit. Documentation should include all visits related to anaphylaxis, allergic reaction(s) or significant symptoms since the previous authorization period.

MOLINA REVIEWER: Compare to baseline or previous authorization period for improvement

AND

☑ Positive response to treatment as documented by at least ONE (1) of the following compared to pre-treatment: [ALL APPLICABLE]
   ☑ Reduction in severe allergic reactions
   ☑ Reduction in epinephrine use
   ☑ Reduction in physician/clinic visits due to peanut allergy (physician office/ER visits/hospitalizations)
   ☑ Improvement in quality of life or productivity

Informational Note: Higher rates of anaphylaxis and use of epinephrine are consistently seen in the treatment groups compared with avoidance alone (Chu et al., PACE 2019). In addition, rates of other types of allergic reactions (e.g., gastrointestinal symptoms, angioedema, wheezing, and eosinophilic esophagitis) are common and are typically higher in patients treated with OIT.

4. Discontinuation of Treatment

Member should be assessed for discontinuation of therapy if ANY of the following are applicable: [ANY]

☐ Member has not experienced unacceptable toxicity, significant non-anaphylactic reaction(s), or anaphylaxis from Palforzia therapy
   ☑ Non-anaphylactic reactions including vomiting, angioedema, and upper and lower respiratory tract reactions
   ☑ 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.

☐ Poor response to treatment as evidenced by physical findings and/or clinical symptoms as per Prescriber’s evaluation and clinical judgement

☐ Contraindications/Exclusions to Palforzia therapy
Authorization will not be granted if ANY of the following conditions apply [ANY]

☑ Non-FDA approved indications
☑ Concurrent use with other peanut desensitization therapy
☑ History of severe or life-threatening episode of anaphylaxis or anaphylactic shock within 60 days
☑ Severe, unstable or uncontrolled asthma
☑ History of cardiovascular disease, including uncontrolled or inadequately controlled hypertension
☑ History of eosinophilic esophagitis and other eosinophilic GI disease
☑ 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 (EoE), other eosinophilic gastrointestinal disease, chronic, recurrent, or severe gastroesophageal reflux disease (GERD), symptoms of dysphagia or recurrent gastrointestinal symptoms of undiagnosed etiology
☑ History of a mast cell disorder, including mastocytosis, urticaria pigmentosa, chronic idiopathic or chronic physical urticaria beyond simple dermatographism (e.g., cold urticaria, cholinergic urticaria), and hereditary or idiopathic angioedema
1. **Recommended Dosage [ONE]**

   Treatment consists of three phases: Initial Dose Escalation, Up-Dosing, and Maintenance

   - Initial Dose Escalation, and the first dose of each Up-Dosing level, are administered under supervision of a healthcare professional in a health care setting, with the ability to manage potentially severe allergic reactions, including anaphylaxis.

   1) **Initial Dose Escalation phase:** Single day dose escalation
      - Administer in sequential order on a single day. Separate each dose by an observation period of 20 to 30 minutes. After completion of Initial Dose Escalation, observe patients for at least 60 minutes prior to discharge.
      - Patients tolerating at least the 3 mg single dose during Initial Dose Escalation must return to the health care setting for initiation of Up-Dosing, preferably the next day. If the patient is unable to return within 4 days, repeat Initial Dose Escalation.

   2) **Up-Dosing phase:** Consists of 11 increasing dose levels and occurs over several months.
      - The first dose of each new Up-Dosing level is administered under the supervision of a health care professional in a health care setting; observe the patient 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.

   3) **Maintenance phase:** Once all Up-Dosing levels are reached, the patient begins a maintenance dose of 300 mg daily.

2. **Authorization Limit [ALL]**

   - Quantity limit: Palforzia is supplied in kits to allow for health care provider clinic/office and patient home administration in accordance with the manufacturer’s recommendations for initial dose escalation, up-dosing, and maintenance dosing phases.
     - Palforzia Initial Dose Escalation Kit 1 kit per fill; one time fill (starting dose, 1 day supply)
     - Palforzia Up-Dosing Kits (Levels 1-11) 1 kit per fill
     - Palforzia 300 mg sachets 1 sachet per day
   - Duration of initial authorization: 6 months
   - Continuation of treatment: Re-authorization for continuation of treatment is required every 6 months to determine continued need based on member meeting ‘Continuation of Therapy’ criteria

3. **Route of Administration [ALL]**

   - Administered orally: The capsule(s) or sachet are opened and the entire dose of Palforzia powder is emptied onto a few spoonfuls of refrigerated or room temperature semisolid food (e.g., applesauce, yogurt, pudding)
   - All Initial Dose Escalation doses and the first doses of each Up-Dosing level must be administered under observation in a certified health care setting
   - May be authorized in a **physician office setting** only. Routine administration in a hospital or outpatient setting will not be authorized
   - If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare.
   - Refer to MHI Policy & Procedure (P&P): Specialty Medication Administration Site of Care Policy: MHI Pharm 11

Consult the manufacturer’s labeling for more detailed information on dosage and administration of this drug, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and monitoring.
**COVERAGE EXCLUSIONS**

This policy only addresses the indication of Palforzia [Peanut (Arachis hypogaea) Allergen Powder-dnfp] when appropriate criteria are met.

All other uses of Palforzia [Peanut (Arachis hypogaea) Allergen Powder-dnfp] that are not an FDA-approved indication or not included in the ‘Coverage Criteria’ section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

*FDA-approved indication does not, in itself, dictate coverage. Molina Clinical Policy may not recommend coverage for all FDA-approved indications. Please review this Policy in its entirety for indications covered by Molina Healthcare.*

**BACKGROUND/SUMMARY**

FDA approval comes from safety and efficacy results from seven clinical studies, including the pivotal Phase 3 PALISADE and RAMSES trials, Phase 2 ARC001 study and the ARC002 open-label follow-on study.

Ongoing studies include ARC004, ARC008 and ARC011. The Phase 3 ARC004 study follow-on study is complete. Study ARC008 is to assess AR101’s safety and tolerability over and extended dosing period.

**EFFICACY**

**PALISADE (Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults)**

(NCT02635776)

Randomized, double-blind, placebo-controlled efficacy and safety study conducted in the United States, Canada, and Europe evaluated how effectively Palforzia improved peanut tolerance in peanut-allergic people ages 4-55. The largest effect was seen in children and teens ages 4-17. There was lack of efficacy seen in adults ages 18-55; however this may be due to small sample sizes in this group since only 41 participants received Palforzia and 14 received placebo.

Inclusion criteria:

- Serum IgE to peanut ≥ 0.35 kUA/L within 12 months before study entry and/or a mean wheal diameter on skin prick test to peanut ≥ 3 mm greater than the negative control
- The primary analysis population was aged 4 through 17 years, 78% white and 57% male
- At study entry, subjects reacted at 100 mg or less of peanut protein in a double-blind, placebo-controlled food challenge (DBPCFC)
- Palforzia treatment also resulted in a reduction in the number and severity of reactions in the exit food challenge, compared to placebo.

Qualifying participants proceeded through 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, during which the dose was 300 mg. The total duration of the trial was approximately 12 months.

Effectiveness was assessed by evaluating the percentage of study participants tolerating a double-blind, placebo-controlled food challenge (DBPCFC) as the primary end point with a single 600 mg dose of peanut protein (twice the daily maintenance dose of Palforzia and equivalent to 2 peanut kernels) with no more than mild allergic symptoms in an exit food challenge at the end of the 6-month maintenance period.
Active group patients were titrated to 300 mg of Palforzia. Among participants 4 to 17 years of age, 250 of 372 participants (67.2%) in the active-drug group were able to ingest a single dose of at least 600 mg of peanut protein (equivalent of 2 peanuts) during the exit food challenge with no more than mild symptoms, as compared with 5 of 124 (4.0%) in the placebo group.

- The study met the primary efficacy endpoint, as 67.2% of patients ages 4–17 tolerated at least a 600-mg dose of peanut protein in the exit food challenge, compared to 4.0% of placebo patients;
- 50.3% patients ages 4–17 tolerated a 1000-mg dose of peanut protein in the exit food challenge, compared to 2.4% of placebo patients;
- Among patients ages 4–17 who completed treatment with AR101, 96.3% tolerated a 300-mg dose of peanut protein in the exit food challenge, 84.5% tolerated a 600-mg dose, and 63.2% tolerated a 1000-mg dose;
- 79.6% patients ages 4–17 completed the trial; of the 20.4% who discontinued treatment, 12.4% withdrew due to treatment-related adverse events.
- Of the 79.6% of those that completed the trial, 96.3% tolerated a 300-mg dose of peanut protein in the exit food challenge, 84.5% tolerated a 600-mg dose, and 63.2% tolerated a 1000-mg dose.
- During the exit food challenge, the maximum severity of symptoms was “moderate” in 25.3% of the participants in the Palforzia group vs. 58.9% of those in the placebo group and “severe” in 5.1% and 10.5%, respectively.
- **Patients in the intervention group actually had an increased rate of severe allergic reactions compared to the control group outside of the clinic (14% vs 3%).**
- This increased risk of side effects largely accounts for the noticeably high number of patients that withdrew during the study: 22% of participants ages 4-17 (80 of 372) and 54% of participants ages 18-55 (22 of 41) who received Palforzia withdrew from the study, compared to 8% of participants ages 4-17 (10 of 124) and 7% of participants ages 18-55 (1 of 14) who received placebo.

The most common adverse events were gastrointestinal (52% abdominal pain, nausea, vomiting) and though the incidence declined in the dose maintenance phase compared with the dose escalation phase, they remained high. Withdrawal rates overall (21.0%) and withdrawals due to adverse events (11.6%) were substantially higher than those observed in the placebo group. Systemic allergic reactions (14.2% vs. 3.2% placebo) and the use of epinephrine (14.0% vs. 6.5% placebo) were more common in the AR101-treated group.

**RAMSES (Real-World AR101 Market Supporting Experience Study in Peanut-Allergic Children)** to evaluate the safety and efficacy of Palforzia in children ages 4-17 without requiring an initial food challenge (NCT03126227) RAMSES is a randomized, double-blind, placebo-controlled safety study conducted in the United States and Canada evaluating Palforzia versus placebo in 506 subjects aged 4 through 17 years with peanut allergy.

Subjects were required to have a clinical history of peanut allergy including onset of characteristic allergic signs and symptoms within 2 hours of known oral exposure to peanut, serum IgE to peanut of ≥ 14 kUA/L and a mean wheal diameter on skin prick test ≥ 8 mm greater than the negative control at screening. Subjects were not required to complete a double-blind, placebo-controlled food challenge (DBPCFC) for study entry (*subjects react at 100 mg or less of peanut protein). The study duration was approximately 6 months and compared the safety and tolerability of Palforzia (N = 337) with placebo (N = 168). Most subjects were male (63%) and white (79%). Of the subjects treated with Palforzia, 60.5% had a medical history of anaphylactic reactions, 65.0% reported multiple food allergies, 57.9% had a medical history of atopic dermatitis, and 52.2% had a present or previous diagnosis of asthma. Subjects with severe persistent or uncontrolled asthma were excluded.
Evidence of Clinical Benefit and Long-Term Effect of Oral Immunotherapy (OIT)

Several randomized trials [Vickery BP, 2017; Varshney P, et al. 2011; Anagnostou K, et al. 2014; Bird JA, et al. 2018; PALISADE Group of Clinical Investigators, 2018; Reier-Nilsen T, et al. 2019] and a number of uncontrolled studies have confirmed that peanut OIT is highly effective in inducing desensitization in a clinical setting; however, OIT increases, rather than decreases, the rate of allergic reactions in the real-world setting.

Short-term sustained unresponsiveness (SU) after discontinuing OIT is much less common than desensitization (Nowak-Węgrzyn; UTD). Data suggest that the development of SU is dose and duration dependent and may also be influenced by the severity of peanut allergy and how early in life OIT is started (Vickery BP, 2017). Longer-term SU is even rarer, and data suggest that ongoing exposure is necessary to maintain the protective effect (POISED study, 2019). The available evidence also suggests that peanut OIT does not improve QOL for the patient while the substantial burden on the patient/caregiver should also be considered.

The Peanut Oral Immunotherapy Study: Safety, Efficacy, and Discovery (POISED; Chinthrajah RS, et al. 2019) trial indicates that the effect of oral immunotherapy (OIT) appears to wane once therapy is discontinued [i.e., it does not appear to induce long-term "sustained unresponsiveness" (SU)]. POISED evaluated 120 patients with peanut allergy in which patients were randomly assigned in a three-way fashion:

- Two years of high-dose peanut OIT (daily dose of 4000 mg), followed by one year of no OIT (group 1, n = 60),
- Two years of high-dose peanut OIT followed by one year of low-dose OIT (daily dose of 300 mg; group 2, n = 35), or
- Three years of placebo (n = 25)

At the two-year mark, 84% of patients in the active therapy groups (groups 1 and 2) were able to pass a 4000 mg peanut challenge compared with 4% in the placebo group. However, the ability to pass the challenge declined considerably during the final year of the trial after stopping or reducing the dose of OIT. At the three-year mark, the rate of passing the peanut challenge among patients who had stopped taking OIT (group 1) was 13%, which was not statistically different than the 4 percent rate in the placebo group. Among patients who continued on low-dose OIT (group 2), 37% passed the challenge at the three-year mark. (POISED; Chinthrajah RS, et al. 2019)

PRACTICE GUIDELINES AND POSITION STATEMENTS

NOTE: The following guidelines were released prior to the FDA approval of Palforzia.

National Institute of Allergy and Infectious Diseases (NIAID) The NIAID issued clinical guidelines on January 5, 2017 regarding the prevention of peanut allergy and these more recent guidelines were an addendum to the 2010 ‘Guidelines for the Diagnosis and Management of Food Allergy’. The guidelines aim to reduce the burden of that stress by reducing the number of people who develop a severe peanut allergy.

The new recommendations are divided into three separate guidelines. Guideline 1 is the recommendations for infants with severe eczema, egg allergy, or both. Infants with these symptoms are most at risk for developing a peanut allergy. Guideline 2 is for infants with moderate eczema, as infants with this symptom still have an elevated risk of developing a peanut allergy. Guideline 3 is for infants that have no eczema or food allergies of any kind. The three guidelines are as follows:

The guidelines recommend that parents introduce their children to peanut butter and peanut containing foods as infants, starting as early as 4-6 months of age, a significant difference from previous recommendations that suggested parents delay exposure to peanut containing foods until the child is much older. The recommendations changed based on the results of clinical trial (Du Toit G et al.) that showed that early consumption of peanut containing foods greatly reduced the risk of developing peanut allergy. According to the NIAID:

‘Recent scientific research has shown that peanut allergy can be prevented by introducing peanut-containing foods into the diet early in life. Researchers conducted a clinical trial called Learning Early About Peanut Allergy (LEAP) with more than 600 infants considered to be at high risk of developing peanut allergy because they had severe eczema, egg allergy, or both. The scientists randomly divided the babies into two groups. One group was given peanut-containing foods to eat regularly, and the other group was told to avoid peanut-containing foods. They did
this until they reached 5 years of age. By comparing the two groups, researchers found that regular consumption of peanut-containing foods beginning early in life reduced the risk of developing peanut allergy by 81 percent.’

Guidelines for the Diagnosis and Management of Food Allergy in the United States (2010)
NIAID Guidelines for the Diagnosis and Management of Food Allergy in the United States (2010) do not recommend OIT for the management of food allergies.

American Academy of Allergy, Asthma & Immunology (AAAAI)
The AAAAI practice parameter for ‘Food Allergy’ (2014) states that OIT shows promise for treating food allergy but is “not ready for implementation in clinical practice at the present time.”

Immunotherapy not recommended in the AAAAI guideline (2014) due to uncertainty whether therapeutic benefit outweighs risk of treatment based on information available at the time, however, several studies published since the guideline appear to have found benefit.

**DEFINITIONS**

Desensitization is defined as an increase in reaction threshold to a food allergen while receiving active therapy, similar to that achieved with drug desensitization. (Nowak-Węgrzyn; UTD)

Oral Immunotherapy (OIT), an allergen-specific approach in the management of food allergies, is based on the administration of increasing doses of the culprit food until reaching a maintenance dose.

**Short-term sustained unresponsiveness (SU)** refers to the ability of a food allergic subject, successfully desensitized with OIT, to pass an oral food challenge (OFC) conducted after stopping the food allergen exposure. SU also refers to retention of the protective benefit achieved through therapy and is not reliant on ongoing exposure. Sustained unresponsiveness has not been adequately studied to provide definitive data.

**CODING INFORMATION:** The codes listed in this clinical policy are for informational purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered. Coverage is determined by the benefit document. This list of codes may not be all inclusive and inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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**REFERENCES**

Package Insert, FDA, Drug Compendia


Clinical Trials, Definitions, Peer-Reviewed Publications


Government Agencies, Professional Societies, and Other Authoritative Publications


