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Policy Number: C18457-A

Palforzia [Peanut (arachis hypogaea) Allergen Powder-dnfp]

PRODUCTS AFFECTED

Palforzia [Peanut (arachis hypogaea) Allergen Powder-dnfp]

COVERAGE POLICY

Coverage for services, procedures, medical devices, and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any. This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
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.

DIAGNOSIS:
Peanut allergy

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by- case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review. The Pharmacy and Therapeutics Committee has determined that the drug benefit shall be a mandatory generic and that generic drugs will be dispensed whenever available.

A. PEANUT ALLERGY:
1. Documented diagnosis of member having a peanut allergy
   AND
2. Documentation of confirmation from a positive skin test OR peanut-specific serum IgE ≥

0.35 kUA/L
AND

3. Documentation member has a history of at least 1 systemic allergic reaction to peanuts requiring hospitalization, an ER visit, or use of injectable epinephrine;
   MOLINA REVIEWER NOTE: Document baseline number in member's authorization since continuation of therapy requests require follow-up documentation as evidence of positive benefit from therapy
   AND
4. Prescriber attests that member will use in conjunction with a peanut-avoidant diet
   AND
5. Member has a current prescription for epinephrine and access to an epinephrine autoinjector while using Palforzia. (Review Rx history)
   AND
6. Prescriber attests or clinical reviewer has found member has NOT experienced severe or life-threatening episode of anaphylaxis or anaphylactic shock in the last 60 days
   AND
7. Prescriber has discussed the adverse effect profile, risks, and burdens of peanut oral immunotherapy (PNOIT) 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)
   AND
8. Documentation of medical justification supports necessity for oral immunotherapy despite peanut avoidance (e.g., member has a severe peanut allergy that can be triggered by smell) [DOCUMENTATION REQUIRED]
   AND
9. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to Palforzia include: uncontrolled asthma, history of eosinophilic esophagitis or other eosinophilic gastrointestinal disease]

CONTINUATION OF THERAPY:

A. PEANUT ALLERGY:

1. Documentation of member re-assessment for this condition to determine if continuation of treatment with requested medication is medically necessary. [DOCUMENTATION REQUIRED]
   AND
2. Documentation of Member's claim history: Any indication of compliance or adherence issues should be discussed with prescriber and clinical pharmacist/medical director for a treatment plan or discontinuation of treatment (Review fill//claim history)
   AND
3. Documentation physician office visits for administration is consistent with FDA-approved labeling schedule
   AND
4. Documentation of 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 to evaluate safety.
   AND
5. Documentation of positive response to treatment as documented by at least ONE of the following compared to pre-treatment to evaluate effectiveness:
   a) Reduction in severe allergic reactions
   b) Reduction in epinephrine use

c) Reduction in physician/clinic visits due to peanut allergy (physician office/ER visits/hospitalizations)
d) Improvement in quality of life or productivity

DURATION OF APPROVAL:
Initial authorization: 12 months; Continuation of Therapy: 12 months

PRESCRIBER REQUIREMENTS:
Prescribed by or in consultation with a 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. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:
Member is 4 to 17 years of age for initial dose escalation OR 4 years of age or older for up-dosing or the maintenance phase of treatment

QUANTITY:
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

PLACE OF ADMINISTRATION:
The recommendation is that oral medications in this policy will be for pharmacy benefit coverage and patient self-administered.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Oral

DRUG CLASS:
Allergenic Extracts/Biologics Misc.

FDA-APPROVED USES:
Indicated 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.
Initial dose escalation may be administered to patients 4 to 17 years of age. Up-dosing and maintenance may be continued in patients 4 years of age and older. 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

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
None

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:

Peanut allergy is an immunoglobulin E (IgE)-mediated allergic response to ingested peanut protein causing severe reactions, including urticaria, hypotension, anaphylaxis, cardiac arrest. Peanut allergy may be a lifelong allergy and the leading cause of anaphylaxis and death due to food allergy. There is no known cure for peanut allergy. Peanut allergy is still managed through peanut avoidance and by carrying emergency medication such as auto injectable epinephrine to treat symptoms that may arise from unintended ingestion (Greenhawt 2020). Despite avoidance, accidental exposure is possible, resulting in unpredictable and potentially severe allergic reactions. Peanut allergy often presents in early childhood affecting an estimated 2% of children in the U.S. (Togias et al., 2017). However, despite avoidance, accidental exposure is possible and may results in unpredictable and potentially severe allergic reactions.

- 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 asymptomatically sensitized and truly allergic patients. Food challenges are time-consuming, labor- intensive, and potentially hazardous, requiring expertise narrowed to certain centers.

- There are no FDA-approved curative treatments and spontaneous resolutions to peanut allergies are rare. The standard of care for peanut allergies has consisted 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 12months of life. Of the infants at high risk of developing a peanut allergy, only 1.9% who were introduced to peanuts early on developed a peanut allergy by age 5 compared to 13.7% 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 overtime
- 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

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 U.S., 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 41participants received Palforzia and 14 received placebo.

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.

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 0.5mg 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.

Active group patients were titrated to 300 mg of Palforzia. Among participants 4 to 17 years of age, 250of 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 a600-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 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) 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 ToitG 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.'

National Institute of Allergy and Infectious Diseases (NIAID)
The use of allergen-specific immunotherapy to treat immunoglobin E–mediated food allergy is not recommended by the NIAID Guidelines for the Diagnosis and Management of Food Allergy in the United States (2010).

American Academy of Allergy, Asthma & Immunology (AAAAI)
There is a general statement addressing the current state of oral immunotherapy (OIT) and Palforzia is noted (2020 Current State of Oral Immunotherapy for the Treatment of Food Allergy); however, the AAAAI has not issued a recommendation regarding Palforzia at this time.

According to a practice parameter (2014) for food allergy (2014), the AAAAI states that OIT shows promise in treating food allergy but is not ready for implementation in clinical practice at the time of publication.

Hayes
According to a Health Technology Assessment, there is insufficient published evidence to assess the safety and/or impact on health outcomes or patient management for use of Palforzia (peanut allergen powder-dnfp) for the management of peanut allergy. The overall quality of the body of evidence was rated 'very low, largely due to the small number of studies, lack of long-term follow-up to assess the durability of benefit and potential safety concerns, and manufacturer involvement in both studies (Rating: D2). The report notes that additional independent studies in a naturalized setting are required to further establish the safety and effectiveness of Palforzia, examine the long-term effect, and identify optimal patient selection criteria for its use.'

Palforzia REMS Program
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.
Notable requirements of the PALFORZIA REMS include the following:

- Health care providers who prescribe PALFORZIA must be certified with the program by enrolling.
- Health care settings must be certified in the program, have on-site access to equipment and personnel trained to manage anaphylaxis, and establish policies and procedures to verify that patients are monitored during and after the Initial Dose Escalation and first dose of each Up-Dosing level.
- Patients must be enrolled in the program prior to initiation of PALFORZIA treatment and must be informed of the need to have injectable epinephrine available for immediate use at all times, the need for monitoring with the Initial Dose Escalation and first dose of each Up-Dosing level, the need for continued dietary peanut avoidance, and how to recognize the signs and symptoms of anaphylaxis.
- Pharmacies must be certified with the program and must only dispense PALFORZIA to health care settings that are certified or to patients who are enrolled depending on the treatment phase.

Further information, including a list of certified prescribers, health care settings, and pharmacies, is available at www.PALFORZIAREMS.com or 1-844-PALFORZ (1-844-725-3679).

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of Palforzia [Peanut (arachis hypogaea) Allergen Powder-dnfp] are considered experimental/investigational and therefore, will follow Molina's Off- Label policy. Contraindications to Palforzia [Peanut (arachis hypogaea) Allergen Powder-dnfp] include: uncontrolled asthma, history of eosinophilic esophagitis or other eosinophilic gastrointestinal disease. 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.

OTHER SPECIAL CONSIDERATIONS:
Palforzia has a Black Boxed Warning for anaphylaxis. Anaphylaxis has been reported during all phases of dosing, including maintenance, and in those who have undergone up-dosing and dose modification procedures. Prescribe injectable epinephrine, instruct, and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. Patients must have their asthma under control prior to initiation of peanut allergen powder- dnfp immunotherapy. Uncontrolled asthma is a risk factor for a serious event, including death, in anaphylaxis. Because of the risk of anaphylaxis, peanut allergen powder is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the *Palforzia* REMS.

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
NA	

AVAILABLE DOSAGE FORMS:
Palforzia Initial Escalation CSPK 0.5 & 1 & 1.5 &3 & 6 MG
Palforzia (300 MG Titration) PACK 300MG
Palforzia (300 MG Maintenance) PACK 300MG
Palforzia (3 MG Daily Dose) CSPK 3 x 1MG
Palforzia (6 MG Daily Dose) CSPK 6 x 1MG

Palforzia (12 MG Daily Dose) CSPK 2 x 1 MG &10 MG
Palforzia (20 MG Daily Dose) CSPK 20MG
Palforzia (40 MG Daily Dose) CSPK 2 x 20MG
Palforzia (80 MG Daily Dose) CSPK 4 x 20MG
Palforzia (120 MG Daily Dose) CSPK 20 MG &100 MG
Palforzia (160 MG Daily Dose) CSPK 3 x 20 MG &100 MG
Palforzia (200 MG Daily Dose) CSPK 2 x 100MG
Palforzia (240 MG Daily Dose) CSPK 2 x 20 MG &2 x 100 MG

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SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements FDA-Approved Uses Appendix Background Other Special Considerations Available Dosage Forms References	Q4 2023
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Appendix Contraindications/Exclusions/Discontinuation References	Q4 2022
Q2 2022 Established tracking in new format	Historical changes on file