In This Issue

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Palforzia® for Mitigation of Peanut Allergy

By: Leighton Boquist, Pharm.D.

Background: The rate of peanut allergy diagnoses in children has nearly tripled in the past two decades to 2.5% of the pediatric population in the U.S., with onset typically occurring in early childhood.[1,2] Due to a lack of an approved treatment for peanut allergy, the standard of care has been a strict avoidance of peanut-based products and the timely administration of rescue medications (e.g., epinephrine) following accidental exposure.[3,4] Previous studies investigating the use of oral immunotherapy (OIT), which employs continual exposure to minute amounts of the peanut allergen to induce desensitization, have been limited by small sample sizes and contrasting methods. Therefore, most practice guidelines do not support the use of OIT in a routine clinical setting. However, there may be a change in standard practice with the approval of peanut (Archis hypogaea) allergen powder-dnf (Palforzia®; Aimmune Therapeutics, Inc.) in January 2020 by the Food and Drug Administration (FDA) for the mitigation of allergic reactions to peanuts in patients 4 through 17 years of age.[5]

Mechanism of Action: It is thought that Palforzia® works through desensitization which occurs when a patient is gradually exposed to increments of an allergen in a controlled setting such as a physician's office.[4,6] However, the exact mechanism of action of this agent is unknown.[5]

Key Clinical Trial: The PALISADE trial evaluated AR101, a peanut-derived biologic OIT, for the treatment of peanut allergy.[4] The study was a phase 3, international, multicenter, randomized, double-blind, placebo-controlled trial. Although participants aged 4 to 55 years with documented peanut allergy were included in the study, the pre-specified primary analysis population

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Safety Alert: Severe GI Hypomotility with Clozapine

By: Atul Dilawri, Pharm.D.

Background: Clozapine (Clozaril®; Novartis Corporation) is an atypical antipsychotic that is approved by the Food and Drug Administration (FDA) for treatment-resistant schizophrenia (TRS), defined as persistent delusions and hallucinations after failing two trials of antipsychotic medications of adequate dose and duration.[1] Clozapine is not recommended first-line for the treatment of schizophrenia due to its serious adverse effects including life-threatening severe neutropenia (absolute neutrophil count [ANC] <500 cells/mL) which mandates routine ANC monitoring under the Clozapine Risk Evaluation and Mitigation Strategy (REMS) program. Constipation is an overlooked, but common side effect of clozapine, with a prevalence rate of 31.2% identified in a meta-analysis that included 2013 clozapine-treated patients.[2] In post-marketing experience, serious and fatal reports of bowel complications have recently strengthened safety concerns regarding clozapine-induced gastrointestinal hypomotility

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included only those aged 4 to 17 years. Participants underwent a double-blind, placebo-controlled food challenge (DBPCFC) at the initial screening. They were eligible for the trial if they had an allergic reaction to ≤100 mg of peanut protein. Those who qualified for the study were randomized to receive either AR101 (n=416) or matching placebo (n=139) in a 3:1 ratio. Treatment started with a 1-day supervised, initial dose escalation phase, which included a five-step dose series from 0.5 mg to 6 mg during a single office visit followed by an increasing-dose phase during which the dose was increased from 3 mg to 300 mg every 2 weeks. After completion of this titration, patients were administered 300 mg daily for a 24-week maintenance phase. At the end of the trial, patients underwent an exit DBPCFC which included exposure to 300 mg, 600 mg, and 1000 mg of peanut protein, as tolerated without manifestation of dose-limiting symptoms. Participants were instructed to follow a strict peanut avoidance diet and carry an epinephrine auto-injector throughout the study. The study's primary outcome was the proportion of patients aged 4 to 17 years who could tolerate a ≥600 mg dose of peanut protein at the exit challenge without experiencing dose-limiting symptoms. Of the participants aged 4 to 17 years, 67.2% of those who received AR101 vs. 4.0% of those who received placebo achieved the primary outcome (difference, 63.2 percentage points; 95% CI, 53.0 to 73.3; P<0.001). The effect was not significant in participants aged 18 to 55 years. However, the sample size may have been too small with only 33 adult participants completing the study. The authors concluded that AR101 showed superiority over placebo in mitigating the severity of peanut allergy symptoms in participants aged 4 to 17 years.

Safety: The overall incidence of adverse effects observed during the intervention period in participants 4 to 17 years old was 98.7% in the treatment group vs. 95.2% in the placebo group.[4] Additionally, there was one case of severe anaphylaxis in the active-drug group during the maintenance phase. Some common adverse effects (occurring in ≥5% of patients) included abdominal pain, cough, dyspnea, pruritus, and anaphylactic reaction.[4,5] Palforzia® is contraindicated in patients with a history of uncontrolled asthma or eosinophilic esophagitis or other eosinophilic gastrointestinal diseases.[5]

REMS Program: The Palforzia® Risk Evaluation and Mitigation Strategy (REMS) program aims to manage the risk of anaphylaxis associated with Palforzia®.[7] Healthcare providers, healthcare facilities, and pharmacies involved with Palforzia® must be certified and patients must be enrolled in this REMS program. Enrolled patients must maintain a peanut-free diet and have injectable epinephrine available at all times. A certified healthcare provider must administer the initial dose escalation regimen and the first dose of each up-dosing level at a certified healthcare facility. Only REMS certified pharmacies may dispense this medication.

Dosing and Administration: Treatment with Palforzia® consists of three sequential phases: initial dose escalation, up-dosing, and maintenance dosing.[5] The initial dose escalation phase is completed during a single office visit in which the patient receives 0.5 mg, 1 mg, 1.5 mg, 3 mg, and 6 mg with a 20 to 30 minute observation period between each dose escalation. If at least a 3 mg dose is tolerated during the initial dose escalation, the patient may enter the up-dosing phase. The up-dosing phase consists of 11 daily dose levels: 3 mg, 6 mg, 12 mg, 20 mg, 40 mg, 80 mg, 120 mg, 160 mg, 200 mg, 240 mg, and 300 mg. No dose level can be skipped during the up-dosing process. The first dose of each level must be given in a physician's office since a 60 minute post-dose observation period is required. Patients must complete 2 weeks of treatment at each dose level. Once the 11th dose level of 300 mg is reached, it is maintained indefinitely since Palforzia® is not curative, and daily doses are needed to maintain desensitization. Before administration, capsules and sachets containing Palforizia® powder should be opened and emptied onto a few spoonfuls of semisolid food (e.g., applesauce, pudding). The powder should not be mixed with a liquid (e.g., milk, water, juice) and never swallowed directly or inhaled. To reduce the risk of an allergic reaction, patients should delay taking Palforzia® after strenuous exercise until the signs of a hypermetabolic state (e.g., flushing, sweating, rapid breathing, rapid heart rate) subside and avoid taking hot showers or baths immediately before or within 3 hours after administration.

Cost and Availability: Palforzia® is available as 0.5 mg, 1 mg, 10 mg, 20 mg, and 100 mg capsules and a 300 mg sachet.[5,8] Various dose kit presentations that contain the appropriate number of doses per level for the initial dose escalation, up-dosing, and maintenance phases are listed in the package insert.[5] The annual cost of maintenance therapy is approximately $13,000.[8]

Formulary Status: Palforzia® was added to the CCHS Pediatric Formulary.

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(CIGH).[3] Reported adverse effects range from constipation to complete bowel obstruction. Gastrointestinal hypomotility caused by clozapine is in part due to its potent anticholinergic activity at M_3 receptors within the gut wall and antagonistic effects at 5-HT3 and H_1 receptors.[1]

FAERS Reports: Between July 2006 and July 2016, there were a total of 10 cases reported to the FDA Adverse Event Reporting System (FAERS) for clozapine-induced constipation that progressed to serious bowel complications resulting in hospitalization or surgery; 5 of the 10 cases resulted in death.[3] Adverse events included necrotizing colitis (n=4), intestinal ischemia or necrosis (n=5), and volvulus (n=1). Total daily doses of clozapine ranged from 200 mg to 600 mg, with a median daily dose of 400 mg. Time to onset of serious bowel complications ranged from 3 days to 6 months with a median onset time of 46 days. A cross-sectional observational study from New Zealand by Every-Palmer and colleagues evaluated CIGH by objectively measuring colonic transit time (CTT) using radiopaque markers.[4] A total of 37 patients were identified of which 20 patients had received clozapine and 17 patients had received non-clozapine antipsychotics. Results from this study demonstrated that clozapine-treated patients had a median CTT over four times longer compared to non-clozapine-treated patients (104.5 hours vs. 23 hours; P<0.0001). Eighty percent of clozapine-treated patients exhibited pan-colonic hypomotility with higher clozapine serum levels being associated with longer transit times. All non-clozapine-treated patients had normal CTT. Overall the authors concluded the effect of clozapine on colonic motility was highly significant and independent of age, gender, dose, and duration of treatment. They also suggested that prophylactic, scheduled (not as needed) laxative treatment should be recommended when initiating clozapine.

Post-Marketing Data: Every-Palmer and Ellis conducted the largest observational study evaluating all reports of serious or life-threatening CIGH adverse reactions received by the Australian and New Zealand pharmacovigilance agencies over a 22-year period from 1992-2013.[5] Of the total 43,132 patients treated with clozapine, 160 (37/10,000) reported having serious CIGH. Constipation and intestinal obstruction were the most commonly reported events, accounting for 47.3% and 41.2% of non-fatal cases, respectively, and 27.6% and 27.6% of fatal cases, respectively. In a subgroup analysis, patients with fatal outcomes had a significantly longer duration of treatment with clozapine than the rest of the group. For every 2 years on clozapine, the odds of a fatal outcome increased by 21% (OR 1.21, 95% CI, 1.02-1.44). Researchers also evaluated international CIGH adverse event data reported to the World Health Organization between 1968-2013 and identified 1335 cases of constipation with 178 fatalities (13%). There were also 698 cases of intestinal obstruction with 177 fatalities (25%). A comprehensive review of 16 studies looking at adverse effects of clozapine identified the incidence rates of agranulocytosis and CIGH to be nearly identical with 3.8–8.0% for agranulocytosis compared with 4.0–8.0% for CIGH.[6] Interestingly, the case-fatality rate was higher with CIGH than with agranulocytosis (15.0–27.5% and 2.2–4.2%, respectively). Overall, consensus from the available literature highlight underdiagnosis and under-treatment of CIGH, likely due to the perception of constipation being a relatively benign adverse effect.

FDA Changes: The FDA required new warnings about the risk of CIGH to be added to the prescribing information of all clozapine products.[3] As of February 2020, the prescribing information for clozapine under section 5 (Warnings and Precautions) was updated to include 'Gastrointestinal Hypomotility with Severe Complications'.[1]

Pharmacist Considerations: Health-care providers should evaluate a patient's bowel function before initiating clozapine and monitor for signs and symptoms of CIGH during treatment.[3,5] If constipation is identified, promptly treat with a laxative, with or without a stool softener. In patients with a history of constipation or bowel obstruction, prophylactic laxative treatment may be considered. Avoid co-prescribing clozapine with other medications that can cause constipation (e.g., anticholinergic agents, opioids). Patients should be counseled on ensuring appropriate hydration, physical activity, and intake of foods high in fiber to prevent constipation.

Formulary Status: Clozapine is on both the Adult and Pediatric CCHS Formularies. Details regarding its restrictions are located in Lexicomp.

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Bamlanivimab	Monoclonal Antibody	COVID-19 Infection	Restricted to adult outpatients 18 years and older who must meet all four of the following: 1. Positive SARS-CoV-2 viral test and symptoms for ≤10 days 2. Not requiring hospitalization or supplemental oxygen or not requiring a change in baseline supplemental oxygen 3. Ordering by select providers in Ohio and Florida 4. Meeting patient criteria below: At least one of the following: i. ≥65 years of age ii. BMI ≥35 iii. Chronic kidney disease (stage 4/5) iv. Diabetes mellitus **OR** ≥55 years of age AND one of the following: i. CD ii. Hypertension iii. COPD/other chronic RD
Casirivimab/ Imdevimab	Monoclonal Antibody	COVID-19 Infection	Same restrictions as bamlanivimab
Ferric derisomaltose (Monoferric®)	Iron Preparation	IDA	Restricted to the Department of Hematology/Oncology for outpatient use only
Ofatumumab (Kesimpta®)	Monoclonal Antibody	Relapsing forms of MS	Restricted to the Department of Neurology for outpatient use only for administration of the first dose
Diclofenac Sodium 1% Topical Gel (Voltaren® Gel)	NSAID	OA of joints	No restrictions

COVID-19=Coronavirus disease 2019 BMI=Body mass index CD=Cardiovascular disease COPD=Chronic obstructive pulmonary disease RD=Respiratory disease IDA=Iron deficiency anemia MS=Multiple sclerosis NSAID=Non-steroidal anti-inflammatory agent OA=Osteoarthritis

Denial to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Denial**
Aprepitant injectable emulsion (Cinvanti®)	Antiemetic	Chemotherapy-induced nausea and vomiting	Due to the significantly higher cost of this agent compared to fosaprepitant and a low incidence of infusion and hypersensitivity reactions with fosaprepitant, Cinvanti® was not added to the CCHS Formulary.

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
4F-PCC (Kcentra®) and aPCC (FEIBA®)	Blood Factors	Various Indications	Modified Restrictions as follows: 1. Remove the need for Staff Surgeon to prescribe 4F-PCC and aPCC for anticoagulant reversal for emergent surgery. 2. Include criteria to allow use of 4F-PCC and aPCC for non-intracranial bleeding secondary to oral anticoagulation: i. Receipt of direct oral anticoagulants (DOAC) within 48 hours (normal renal function), or 72-96 hours (acute kidney injury), or receipt of warfarin with INR ≥ 2; AND one of the following: 1. Bleeding at a critical site: a. Spinal b. Intraocular c. Pericardial d. Airway: hemoptysis with shortness of breath or hypoxia, posterior epistaxis e. Hemothorax f. Intra-abdominal (non-GI) g. Retroperitoneal h. Intramuscular i. Intra-articular 2. Bleeding at a non-critical site that is unresponsive to conventional measures (e.g., 4 units FFP, 1 unit platelets, and 10 units cryoprecipitate), contraindication to large volume resuscitation, or inadequate blood product availability) Including one of the following: a. Hemoglobin decrease ≥ 5 g/dL, or administration of multiple units of red blood cells (RBCs) b. Hemodynamic instability (e.g., SBP< 90 mmHg or MAP <65 mmHg, or requiring vasopressors)*
Chloroquine Tablets	Antimalarial	Chronic Disease States and Malaria	Modified restrictions to include: Restricted to the treatment of chronic disease states or malaria. Removed the indication of confirmed COVID-19 infection.
Darbepoetin alfa (Aranesp®)	Colony Stimulating Factor	Anemia	Modified restriction to include: The treatment of anemia when BNAO (e.g., Jehovah's Witness patients who refuse blood products)

*NOTE: Current guidelines for 4F-PCC and a-PCC for intracranial hemorrhage will remain in place. A link to the Oral Anticoagulant-Related Intracranial Hemorrhage Reversal Algorithm will also be located in the restriction criteria for easier access.

4F-PCC=Four factor protein complex concentrate aPCC=Activated protein complex concentrate INR=International normalized ratio GI=Gastrointestinal FFP=Fresh frozen plasma SBP=Systolic blood pressure MAP=Mean arterial pressure COVID-19=Coronavirus disease 2019 BNAO=Blood is not an option

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Denosumab (Xgeva®)	Monoclonal Antibody	Hypercalcemia	Modified restriction to include: Inpatients or outpatients experiencing hypercalcemia (corrected serum calcium >12 mg/dL) in whom IV bisphosphonates are contraindicated (e.g., severe renal dysfunction)
Diclofenac Epolamine 1.3% topical patches (Flector®)	NSAID	Pain Relief	Removed restrictions on diclofenac epolamine 1.3% topical patches
Eculizumab (Soliris®)	Monoclonal Antibody	Various Indications	Modified restriction to include: Staff Physicians from the Department of Hematology/Oncology.
Epoetin alfa (Procrit®)	Colony Stimulating Factor	Anemia	Modified restriction to include: For the treatment of anemia when BNAO
Ferric carboxymaltose (Injectafer®)	Iron Preparation	IDA	Injectafer® has been removed from use by the Department of Hematology/Oncology for adult patients. Injectafer® will remain on formulary for use by the Department of Nephrology and Outpatient Blood Management Program for outpatient use only.
Hydroxychloroquine (Plaquenil®)	Antimalarial Agent	Chronic Disease States and Malaria	Modified restriction to remove the indication of confirmed COVID-19 infection. The updated restriction criteria will read: Restricted to the treatment of chronic disease states or malaria.
IV Chlorothiazide (Diuril®)	Diuretic	Edema	Removed restrictions
Lopinavir/Ritonavir (Kaletra®)	Antiretroviral	HIV Infection	Modified restrictions to include: Restricted to the treatment of HIV infection. Removed the indication of COVID-19 infection.
Naltrexone IM Injection (Vivitrol®)	Opioid Antagonist	Alcohol Abuse Disorder	Modified restrictions to include: The Department of Psychiatry.
Ravulizumab (Ultomiris®)	Monoclonal Antibody	Paroxysmal Nocturnal Hemoglobinuria	Modified restriction to include: Staff Physicians from the Department of Hematology/Oncology.
Rituximab (Rituxan® and biosimilar)	Monoclonal Antibody	Various Indications	Modified restriction to include: The Department of Dermatology for the treatment of non-malignant dermatologic indications (e.g., pemphigus vulgaris) in outpatients
Subcutaneous Rituximab and Hyaluronidase (Rituxan Hycela®)	Monoclonal Antibody	Various Indications	Removed restrictions stating that B-cell lymphoma does not include Waldenstrom's macroglobulinemia or PCNSL. Use in PCNSL will require prior authorization prior to initiating treatment.

IV=Intravenous NSAID=Nonsteriodal anti-inflammatory drug BNAO=Blood is not an option IDA=Iron deficiency anemia
HIV=Human immunodeficiency virus COVID-19=Coronavirus disease 2019 IM=Intramuscular CNS=Central nervous system
PCNSL=Primary central nervous system lymphoma

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Tadalafil (Adcirca®)	Phosphodiesterase-5 Enzyme Inhibitor	PAH BPH Raynaud's phenomenon	Modified restrictions to include: Continuation of home therapy
Tranexamic acid tablets (Lysteda®)	Hemostatic Agent	Management or prevention of bleeding due to disease-related or chemotherapy-induced thrombocytopenia	Modified restriction to include: The Department of Hematology/Oncology

PAH=Pulmonary arterial hypertension BPH=Benign prostatic hypertrophy

Product Standardizations of the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Standardization**
Cetirizine (Zyrtec®) Fexofenadine (Allergra®)	Antihistamine	Various Indications	A therapeutic interchange for second generation oral antihistamines was approved. Various second generation antihistamines will be automatically converted to either cetirizine as a preferred choice or fexofenadine as an alternate choice; combination second generation antihistamines with pseudoephedrine will be automatically converted to either either cetirizine or fexofenadine with pseudoephrine. Details of this therapeutic interchange will appear in Epic and Lexicomp

Process Changes of the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Process Change**
aPCC (FEIBA®)	Blood Factor	Various Infections	Dose rounding policy: Doses <250 units will be rounded down and doses ≥250 will be rounded up (e.g., a 4,100 unit dose will be rounded down to 4,000 units and a 4,250 unit dose will be rounded to 4,500 units)

aPCC=Activated protein complex concentrate

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
23.4% Sodium Chloride	Electrolyte	Intracranial Hypertension Traumatic Brain Injury	Restricted to ICUs only (Emergency Departments and Operating Rooms are considered ICUs) a. Must be ordered by Neurosurgery Staff or ICU/ED Staff with Neurosurgery consult for refractory intracranial hypertension or traumatic brain injury via order panel/ set b. Restricted to patients with ICP >20 mmHg despite 3% sodium chloride bolus and 3% sodium chloride infusion, or active herniation with presumed ICP >20 mmHg
Methylnaltrexone (Relistor®)	Opioid Antagonist	Opioid-induced Constipation	Restricted to the Departments of Gastroenterology, Pain Management, Hematology/Oncology, and Pediatric ICU for use in patients currently on opioid therapy who have failed at least two other scheduled (e.g., not PRN) and administered laxative agents for 48 hours, or patients who are NPO. Patients will be limited to two doses of methylnaltrexone.

ICU=Intensive care unit ED=Emergency department ICP=Intracranial pressure PRN=As needed NPO=Nothing by mouth

Removal from the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Reason for Removal**
Magnesium chloride (SLO-MAG®), Magnesium gluconate (MAG-G®) Magnesium oxide (URO-MAG®)	Magnesium Supplement	Hypomagnesemia	Rationale: SLO-MAG®, MAG-G®, and URO-MAG® were removed from the CCHS Pediatric Formulary as part of the oral magnesium supplement standardization initiative. Magnesium oxide (MAG-OX®) and magnesium lactate (MAGTAB ER®) will remain on Formulary.

Changes in Restrictions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Alteplase (Activase®)	Thrombolytic Agent	Stroke	Modified restrictions to include: When used for treating stroke, alteplase use is restricted to the following prescribers: Pediatric Neurology Staff, Pediatric ICU Staff with Pediatric Neurology Staff consult, and Emergency Department Staff with Pediatric Neurology Staff consult
Loratidine (Claritin®)	Antihistamine	Bone Pain	Modified restrictions to include: Restricted for treatment of bone pain secondary to G-CSFs
Repository Corticotropin (Acthar® Gel)	Adrenocorticotropin Stimulating Hormone	Infantile Spasms	Modified restrictions to include: Prior Authorization MUST be obtained from the patient's insurance company prior to initiating therapy in both inpatient and outpatient settings. Continuation of therapy from home is not restricted.

ICU=Intensive care unit G-CSF=Granulocyte colony-stimulating factor

Product Standardization to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Standardization**
Cetirizine (Zyrtec®) Fexofenadine (Allergra®)	Antihistamine	Various Indications	Second generation oral antihistamine therapeutic interchange: Please see Adult CCHS Product Standardization section. Lexicomp and Epic have further details.
Magnesium Oral supplements	Electrolyte	Hypomagnesemia	A therapeutic interchange for oral magnesium supplements was approved. Lexicomp and Epic have further details.