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Afamelanotide for Erythropoietic Protoporphyria

By: Rick Carlson, Pharm.D.

Background: Erythropoietic protoporphyria (EPP) is a rare, inherited metabolic disorder characterized by a deficiency of the enzyme ferrochelatase, leading to an accumulation of protoporphyrin in the plasma and blood cells.[1] Increased levels of protoporphyrin cause severe reactions to sunlight and some types of artificial light. Patients with EPP experience severe pain, tingling, itching and/or burning of the skin when exposed to sunlight. Lifestyle modifications, including avoiding sunlight, wearing sunscreen, and protective clothing, were previously the only proven ways to avert the debilitating effects of EPP. However, in October 2019, the Food and Drug Administration (FDA) approved afamelanotide (Scenesse®; Clinuvel, Inc.) to increase pain-free light exposure in adult patients with a history of phototoxic reactions from EPP.

Mechanism of Action: Afamelanotide is an agonist for the melanocortin receptor (MCR), preferentially binding to MC1-R.[2,3] Stimulation of the MCR causes increased eumelanin production, which helps prevent ultraviolet (UV) light radiation damage that occurs in EPP.[4]

Clinical Trials: The safety and efficacy of afamelanotide were assessed in two phase III, multicenter, randomized, double-blind, placebo-controlled trials: one performed in the European Union (EU) and the other in the United States (US).[4] For both studies, patients were included if they were ≥18 years old and had EPP without a history of skin cancer or drug or alcohol abuse. Select exclusion criteria were pregnancy and hepatic dysfunction. A total of 168 patients were enrolled in both trials (74 in the EU trial and 94 in the US trial). The

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Zolgensma® for Spinal Muscular Atrophy

By: Luke Mennen, Pharm.D., MBA

Background: Spinal muscular atrophy (SMA) is a rare, fatal childhood disorder caused by the lack or dysfunction of the gene that encodes survival motor neuron 1 (SMN1), the primary gene responsible for survival motor neuron (SMN) protein production.[1] Infants with this genetic abnormality have hypotonia, severe weakness, and cannot sit up without support. Type 1 SMA (SMA1) is the most common and severe form of this disease with patients typically having two copies of the survival motor neuron 2 (SMN2) gene which are associated with a significantly lower production of the SMN protein than the SMN1 gene. Symptoms of SMA1 may appear at birth or by at least 6 months of age. In December 2016, the Food and Drug Administration (FDA) approved nusinersen (Spinraza®; Biogen), the first pharmacologic treatment for SMA in pediatric and adult patients.[2] This intrathecal medication, an SMN2-directed antisense oligonucleotide,

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main difference in the US trial compared to the EU trial was duration of treatment (6 months vs. 9 months, respectively). Thus, patients in the US trial received three doses of study medication vs. five doses in the EU trial. Additionally, most of the study period in the US trial occurred during the summer months and the primary outcome was assessed while patients were in direct sunlight vs. sunlight and shade in the EU trial. Following the withdrawal of one patient from the trial, the rest were randomized to receive afamelanotide 16 mg subcutaneous implant (n=86) or placebo implant (n=81) at week 0 and every 8 weeks thereafter. The primary outcome was the duration of direct sunlight exposure without pain between 10 a.m. and 3 p.m. in the EU trial and between 10 a.m. and 6 p.m. in the US trial. Select secondary outcomes included the number of phototoxic reactions and quality of life (QoL). Pain was rated on an 11-point Likert pain-intensity scale (with scores ranging from 0 to 10; higher scores indicating greater severity of symptoms). Quality of life scores were measured on a 0 to 100 Likert scale, with higher scores indicating a better QoL. The primary outcome of sunlight exposure duration without pain was 69.4 hours for afamelanotide vs. 40.8 hours for placebo in the US trial (p=0.04) and 6.0 hours for afamelanotoide vs. 0.8 hours for placebo in the EU trial (p=0.005). In the EU trial, a statistically significant difference was found favoring afamelanotide over placebo concerning the number of phototoxic reactions after 9 months (77 vs. 146, respectively; p=0.04) and the QoL score at day 120 (78.8 vs. 63.6, respectively; p=0.005). In the US trial, afamelanotide showed significant improvement in the QoL score compared with placebo at day 120 (49.8 vs. 30.4, respectively; p<0.001), but no significant difference in the number of phototoxic reactions after 6 months (46 vs. 43, respectively; p=0.60). The most common side effects were headache, nausea, nasopharyngitis, and back pain. There were no clinically relevant between-group differences in the incidence or severity of side effects. The authors concluded that afamelanotide had an acceptable safety profile and improved tolerance to UV radiation in patients with EPP, improving their QoL.

Safety: The most common adverse events occurring in the afamelanotide group vs. placebo group in the clinical trials were implant site reactions (21% vs. 10%, respectively) and nausea (19% vs. 14%, respectively).[2,3] Other side effects occurring in >2% of the active treatment group were oropharyngeal pain, cough, fatigue, dizziness, skin hyperpigmentation, somnolence, melanocytic nervus, respiratory tract infection, non-acute porphyria, and skin irritation. Darkening of pre-existing nevi and ephelides may occur. Consequently, a full-body skin examination is recommended twice a year to monitor pre-existing and new skin pigmentary lesions.

Dosing and Administration: A single afamelanotide 16 mg controlled-release implant is inserted subcutaneously above the anterior supra-iliac crest every 2 months via sterile technique.[2,3] Before receiving afamelanotide, patients must be assigned a unique identifier number from Clinuvel, Inc.[5] Implants may only be inserted at certified EPP centers by certified healthcare professionals who have completed training sponsored by the manufacturer.

Cost and Availability: Afamelanotide is available as a 16 mg single dose sterile rod implant (NDC 73372-0116-1) with an average wholesale price of $54,123.[6] The annual cost of therapy is approximately $325,000.

Formulary Status: Afamelanotide is currently on the CCHS Adult Formulary restricted to the Department of Dermatology at Main Campus and to specific physicians (Drs. Arbesman, Matyin, and Vidimos).

References:

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helps increase SMN protein production. In May 2019, onasemnogene abeparvovec-xioi (Zolgensma®; AveXis, Inc), a novel SMA therapy, was FDA-approved for the treatment of pediatric patients <2 years of age with SMA with bi-allelic mutations in the SMN1 gene.[3]

Mechanism of Action: Spinal muscular atrophy is caused by a bi-allelic mutation in the SMN1 gene that causes insufficient SMN protein expression.[3] To offset this aberration, Zolgensma®, a recombinant adeno-associated virus 9 (AAV9)-based gene therapy, is designed to deliver a functional copy of the gene encoding for the SMN protein.

Key Clinical Trials: The safety and efficacy of Zolgensma® were evaluated in the START trial.[1] It was a prospective, single-center, 24-month post-dose phase 1 study conducted from May 2014 to August 2017. The study enrolled infants with the onset of SMA1 at birth up to 6 months of age with two copies of the SMN2 gene and visible SMA symptoms. Patients (N=15) received a one-time intravenous (IV) low dose (6.7×10^{13} vector genomes [vg] per kilogram [kg] of body weight) (cohort 1; n=3) or high dose (2.0×10^{14} vg/kg) (cohort 2; n=12) of Zolgensma®. The mean age of individuals in cohorts 1 and 2 were 6.3 months and 3.4 months, respectively. The primary outcome was safety based on any treatment-related adverse events of grade 3 or higher. The secondary outcome was the time until death or the need for permanent ventilator assistance. Exploratory outcomes looked at motor-milestone achievements (particularly, sitting unassisted) and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scores. The CHOP INTEND scale measures milestones in motor function with scores ranging from 0 to 64, higher scores indicating better motor function. There were a total of 56 serious adverse events observed across both cohorts. Two treatment-related grade 4 events were elevated hepatic enzymes, which were resolved with prednisolone. All 12 high-dose and two of the three low-dose patients were alive without requiring permanent ventilator support at 24 months of follow-up, compared with only 8% of patients in an untreated, historical cohort at 20 months of age. Seventy-five percent (9/12) of high-dose patients achieved functional independent sitting for ≥30 seconds at 24 months of follow-up. Cohort 2 patients had a mean increase of 24.6 points from a mean baseline of 28.2 points and 92% (11/12) of these patients achieved a CHOP INTEND >40 points. Patients in cohort 1 experienced limited motor-milestones and did not reach a CHOP INTEND score >40. No patients in an untreated, historical cohort had achieved any of these motor-milestones and rarely reached a CHOP-INTEND score >40. The investigators concluded that for patients with SMA1, a single IV infusion of Zolgensma® resulted in longer survival, superior achievement of motor-milestones, and better motor function than in the historical cohorts. The safety and efficacy of Zolgensma® were also assessed in the STR1VE trial, a phase 3, open-label, multicenter study conducted in the US.[4] An IV infusion of Zolgensma® of 1.1×10^{14} vg per kg of body weight was administered over 1 hour. Most infants with pre-symptomatic SMA or type 1 SMA who were treated with Zolgensma® experienced survival without the need for permanent ventilator support and 59% were able to sit unassisted for ≥30 seconds at 18 months of age, unlike the untreated historical cohort.

Safety: Zolgensma® has a black boxed warning for acute serious liver injury.[3] The most common adverse effects (≥5%) were elevated aminotransferases and vomiting. Before initiating therapy, liver function should be assessed by clinical exam and laboratory testing.

Dosing and Administration: The recommended one-time dose of Zolgensma® is 1.1×10^{14} vg/kg.[3] It should be administered as an IV infusion over 60 minutes. Starting one day before the infusion, it is recommended that patients receive systemic corticosteroids equivalent to oral prednisolone at 1 mg/kg/day for a total of 30 days. Liver function should be assessed by clinical examination and laboratory testing at the end of this systemic corticosteroid treatment.

Cost and Availability: The cost of a single Zolgensma® infusion is $2,125,000 versus Spinraza®, an intrathecal infusion with a wholesale acquisition cost of $805,000 for the first year of therapy and $380,000 per year thereafter.[5] Zolgensma® is shipped frozen as a customized kit.[3] Upon receipt, it should be stored in a refrigerator at 2˚C to 8˚C (36˚F to 46˚F) and must be used within 14 days; it cannot be refrozen. A list of the kit sizes containing the number of vials per weight ranges and their corresponding NDC numbers are available in the package insert.

Formulary Status: Zolgensma® was added to the CCHS Pediatric Formulary restricted to Staff Physicians from the Department of Pediatric Neurology in patients who meet the following criteria:

1) Outpatients <2 years of age with SMA type 1
2) Only after prior authorization has been obtained from the patient's insurance company

References:

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Additions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Aripiprazole Lauroxil/ Aripiprazole Lauroxil Nanocrystal Dispersion (Aristada®/Aristada Initio®)	Antipsychotic	Schizophrenia	Restricted to the Department of Psychiatry for initiation of therapy Continuation of home therapy is not restricted
Baricitinib (Olumiant®)	Janus Kinase Inhibitor	COVID-19 Infection	Please refer to Lexicomp for details regarding the most current restrictions
Cenobamate (Xcopri®)	Anticonvulsant	Focal Seizure	Restricted to the Department of Epilepsy for initiation of therapy for uncontrolled focal seizures Continuation of home therapy is not restricted
Icosapent Ethyl (Vascepa®)	Antilipemic Agent	Hypertriglyceridemia	No restrictions
Idecabtagene Vicleucel (Abecma®)	CAR-T Immunotherapy	Relapsed/Refractory Multiple Myeloma	Restricted to the Depart-ments of Hematology and Oncology and Bone Marrow Transplantation
Lonacastuximab Tesirine-lypl (Zynlonta®)	Monoclonal Antibody	Relapsed/Refactory Large B-Cell Lymphoma	Restricted to the Department of Hematology/Oncology for outpatient use only
Rotigotine Transdermal Patch (Neupro®)	Dopamine Agonist	Parkinson's Disease Restless Legs Syndrome	Restricted to the Department of Neurology for initiation of therapy Continuation of home therapy is not restricted

COVID-19=Corona virus disease 2019 CAR-T=Chimeric antigen receptor-T cell

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Brexanolone (Zulresso®)	GABA-A Receptor Positive Modulator	Post-partum Depression	Modified restriction to include specific physicians at Hillcrest (Drs. Ken Rao, Lara Feldman, Vrashali Jain, and Adele Viguera) and Fairview (Dr. Katie Taljan) per the Brexanolone IV Infusion Time Limited Protocol (including a qualifying 17-item Hamilton Rating Scale for depression score ≥ 20). Both Psychiatry and Obstetrics will evaluate the appropriateness of therapy before initiating treatment. The Brexanolone IV Infusion Time Limited Protocol will be amended to not awake patients at night as long as continuous pulse oximetry is in place
Casirivimab/ Imdevimab	Monoclonal Antibody	COVID-19 Infection	Please refer to Lexicomp for details regarding the most current restrictions

GABA=Gamma amino butyric acid IV=Intravenous COVID-19=Corona virus disease 2019

Changes in Restrictions to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Ferric Derisomaltose (Monoferric®)	Iron Preparation	Iron Deficiency Anemia	Modified restrictions to include use by the Anemia Management Clinic for outpatient use only Injectafer® will be removed from use by the Anemia Management Clinic
Rituximab-pvvr (Ruxience®)	Monoclonal Antibody	Various Indications	Modified restrictions to include: Restricted to General Neurology Staff Physicians and Neuro ICU Staff Physicians for the inpatient management of autoimmune encephalitis, neuromyelitis optica, and multiple sclerosis following steroids and either IVIG or plasma exchange
Tocilizumab (Actemra®)	Monoclonal Antibody	Cytokine Release Syndrome	Modified restriction criteria for the Department of Infectious Diseases in COVID-19 positive patients to clarify that the CRP must be at least 7.5 mg/dL within 24 hours of tocilizumab administration*

*Tocilizumab should not be used with a kinase inhibitor for COVID-19 therapy
ICU=Intensive care unit IVIG= Intravenous immune globulin COVID-19=Corona virus disease 2019 CRP=C-reactive protein

Product Standardizations of the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
$Alpha_2$ Agonist Ophthalmic Agents	$Alpha_2$ Agonist	Various Indications	A therapeutic interchange was approved to convert apraclonidine 0.5% ophthalmic solution and brimonidine 0.1%, and 0.15% ophthalmic solutions to brimonidine 0.2% ophthalmic solution*†
Beta-Blocker Ophthalmic Agents	Beta-Blocker	Various Indications	A therapeutic interchange was approved to convert all beta-blocker ophthalmic agents to timolol maleate 0.5% ophthalmic solution*
Corticosteroid Ophthalmic Agents	Corticosteroids	Various Indications	A therapeutic interchange was approved to convert various corticosteroid ophthalmic agents prednisolone acetate 1% suspension*‡
Miotic Ophthalmic Agents	Cholinergic Agents	Various Indications	A therapeutic interchange was approved to standardize to pilocarpine 1% and 4% ophthalmic solutions*
Mydriatic Ophthalmic Agents	Anticholinergic Agents	Various Indications	A therapeutic interchange was approved to standardize to the following ophthalmic solutions: atropine 1%, cyclopentolate 1%, tropicamide 1%, and phenylephrine 2.5%*
Non-steroidal Anti-inflammatory Ophthalmic Agents	NSAID	Various Indications	A therapeutic interchange was approved to convert all NSAID ophthalmic agents to ketorolac 0.5%*

*Details are in Lexicomp
†Apraclonidine 1% solution will remain for outpatient Cole Eye use. Brimonidine 0.025% will remain non-formulary/non-stock.
‡Difluprednate 0.05% suspension and fluorometholone 0.1% suspension will be maintained
NSAID=Non-steroidal anti-inflammatory drug

Product Standardizations of the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Benign Prostatic Hypertrophy Agents (Oral)	$Alpha_1$ Adrenoceptor Antagonist	Benign Prostatic Hypertrophy	A therapeutic interchange was approved to convert selective $alpha_1$ adrenoreceptor antagonists (e.g., silodosin) to tamsulosin and non-selective $alpha_1$ adrenoceptor antagonists (e.g., alfuzosin, terazosin) to doxazosin*
Omega-3-acid Ethyl Esters (Lovaza®)	Antilipemic	Hypertriglyceridemia	A therapeutic interchange was approved to convert Lovaza® to Vascepa®*
Over-Active Bladder Agents (Oral and Transdermal)	Anti-muscarinic Agents	Over-Active Bladder	A therapeutic interchange was approved to convert various overactive bladder agents to trospium IR 20 mg*
Rifaximin	Rifamycin	Various Indications	A therapeutic interchange was approved to convert all orders for rifaximin 200 mg, 400 mg, and 600 mg to rifaximin 550 mg* All formulary restrictions for rifaximin were removed

*Details are in Lexicomp

Denials and Removals to the Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Rationale**
Aducanumab (Aduhelm™)	Monoclonal Antibody	Alzheimer's Disease	Aducanumab was denied addition to the CCHS Formulary based on available data
Fish Oil Products (OTC and Dietary Supplements)	Antilipemic	Hypertriglyceridemia	Removed due to questionable efficacy*
Omega-3-acid Ethyl Esters (Lovaza®)	Antilipemic	Hypertriglyceridemia	Lovaza® was removed from the CCHS Formulary Please see Product Standardization section
Rilonacept (Arcalyst®)	Interleukin-1 Inhibitor	Recurrent Pericarditis	Rilonacept was denied addition to the CCHS Formulary due to its significant cost compared to anakinra†

*Note: If patients are admitted on non-prescription fish oil products, those products will be discontinued for the inpatient admission and prescription fish oil products (e.g. , Vascepa®) will not be substituted.

†Patients who require treatment with rilonacept and are currently admitted will be started on anakinra inpatient and enrolled in the rilonacept Quick Start Program to coordinate outpatient access to the medication.

Additions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Baricitinib (Olumiant®)	Janus Kinase Inhibitor	COVID-19 Infection	Please refer to Lexicomp for details regarding the most current restrictions
Galsulfase (Naglazyme®)	Enzyme	MPS VI	Restricted to outpatient use only
Ivabradine (Corlanor®)	Cardiovascular Agent	Heart Failure	Restricted as follows: 1) Initiation of ivabradine is restricted to the Department of Pediatric Cardiology 2) Continuation of therapy is not restricted

MPS=Mucopolysaccharidosis VI

Product Standardizations and Process Changes to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Comments**
Acetaminophen (Ofirmev®) (IV)	Analgesic	Pain Reliever	Doses of IV acetaminophen will be automatically rounded to 500 mg for patients weighing 35 kg to <45 kg
Oxymetazoline/ Phenylephrine Nasal Spray/ Nasal Drops	Decongestant	Nasal Congestion	Phenylephrine 0.25%, 0.5%, and 1% nasal sprays will be removed from the CCHS Pediatric Formulary and interchanged as follows: Patients <6 years of age will be automatically converted to phenylephrine 0.125% nasal drops -1 drop in each nostril every 2-4 hours as needed* Patients ≥6 years of age will be automatically converted to oxymetazoline 0.05% nasal spray -2 to 3 sprays into each nostril twice daily for ≤3 days
Potassium Chloride (IV)	Electrolyte	Hypokalemia	Doses of IV intermittent potassium chloride will be automatically rounded for pediatric patients weighing >2 kg †

*Oxymetazoline is not recommended for use in children <6 years of age (especially in infants).
†Previously rounding occurred for patients weighting >3kg
IV=Intravenous

Changes in Restrictions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Anti-inhibitor Coagulant Complex (FEIBA®)	Blood Derivative	Hemophilia DOAC Reversal	Modified restrictions to: Hemophilia Management: Restricted to the Department of Pediatric Hematology/ Oncology Direct Oral Anticoagulant Reversal (e.g., rivaroxaban) according to the guideline for the initial dose. Hematology consult should occur for subsequent doses.*†
Dextroamphetamine/ Amphetamine (Adderall®/ Adderall XR®)	Amphetamine	ADHD	Modified restrictions to: Initiation of dextroamphetamine and amphetamine is restricted to the Child and Adolescent Psychiatry. Continuation of therapy from home if clinically necessary is not restricted
Diazepam Rectal Gel (Diastat®)	Benzodiazepine	Seizures	Modified restrictions to: Rectal diazepam (Diastat®) use is restricted to pediatric patients ≥6 months of age AND ≥10 kg. It may be ordered by any service. Use of rectal diazepam (Diastat®) in pediatric inpatients <6 months of age OR <10 kg is restricted to Staff Physicians from Pediatric Epilepsy or Pediatric Neurology
Fat Emulsion (Fish Oil and Plant Based) (Smoflipid®)	Caloric Agent	Fatty Acid Supplement	Modified restrictions to: Use of Smoflipid® in the NICU or in the neonatal population (0-28 days of life) regardless of location is not restricted. Initiation of Smoflipid® outside of the NICU in anyone >28 days of life (i.e.,non-neonatal population) is restricted to Pediatric Gastroenterology Continuation of therapy (e.g., transferred from inpatient to Shaker Rehab Campus) is not restricted

*For DOAC-related intracranial hemorrhage refer to Pediatric DOAC reversal guideline.
†For DOAC-related NON-intracranial hemorrhage refer to the Criteria for FEIBA for DOAC-related NON-INTRACRANIAL Bleeding Document.
DOAC=Direct oral anticoagulant inhibitor ADHD=Attention deficit hyperactivity disorder NICU=Neonatal intensive care unit

Changes in Restrictions to the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restrictions/Comments**
Gentamicin Ophthalmic Ointment (Gentak®)	Antibiotic	Ophthalmic Infections	Modified restrictions to: Restrict use to patients >28 days (non-neonatal population)
Guanfacine Extended-Release (Intuniv®)	Alpha$_2$ Adrenergic Agonist	ADHD	Modified restrictions to: Initiation of guanfacine extended-release is restricted to the Department of Child and Adolescent Psychiatry Continuation from home is not restricted
Melatonin	Dietary Supplement	Sleep Aid	Removed all restrictions
Tocilizumab (Actemra®)	Monoclonal Antibody	Cytokine Release Syndrome	Please refer to the Adult Changes in Restrictions Table

ADHD=Attention deficit hyperactivity disorder

Removal from the Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Rationale**
Phenylephrine 0.25%, 0.5% and 1% Nasal Drops	Decongestant	Nasal Congestion	Please refer to the nasal decongestant therapeutic interchange in the Pediatric Product Standardizations and Process Changes Table