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Formulary Information

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Alglucosidase alfa for Pompe Disease

By: Kajal Patel, Pharm.D.

What is Pompe disease? Pompe disease, also known as acid maltase deficiency or glycogen storage disease type II, is an inherited autosomal recessive disorder involving an absence or deficiency of acid alpha glucosidase (GAA).[1] Acid alpha glucosidase normally hydrolyzes lysosomal glycogen to glucose. A deficiency in GAA results in lysosomal accumulation of glycogen, primarily in muscle tissues, which ultimately leads to myopathies.

What is the difference between infantile-onset and late-onset Pompe disease? Due to the variability in clinical manifestation, Pompe disease is divided into two general subtypes: infantile-onset and late-onset.[1] These subtypes are based on the age of onset, rate of disease progression, and extent of organ involvement. Infantile-onset Pompe disease is characterized by a rapidly progressive syndrome presenting as hypertrophic cardiomyopathy, generalized muscle weakness, and hypotonia in the first few months of life.[1] Death, which usually occurs by year 1 if untreated, is most commonly due to cardiorespiratory failure. Late-onset Pompe disease is characterized by a slowly progressive myopathy typically involving skeletal muscle (proximal and respiratory) and usually presents in the second to sixth decade of life.[1] As skeletal muscles progressively weaken, patients may become wheelchair-bound and require ventilator support. Cardiac muscle is generally spared and respiratory failure is the most common cause of death for this subtype.

What agents are available to manage Pompe disease and are they interchangeable? Myozyme® and Lumizyme®, which are both manufactured by Genzyme Corporation, are

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Macitentan for Pulmonary Arterial Hypertension

By: Christopher Domenico, Pharm.D.

Introduction: Pulmonary arterial hypertension (PAH) is a disease characterized by restricted blood flow through the pulmonary arterial circulation leading to increased pulmonary vascular resistance and subsequently right heart failure.[1] The prognosis of PAH is poor, with approximately a 15% mortality rate within the first year of starting therapy. Both the European Society of Cardiology (ESC)/European Respiratory Society (ERS) and American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend endothelin receptor antagonists as first-line therapy in patients with mild to moderate PAH. Macitentan (Opsumit®, Actelion), an endothelin receptor antagonist, is approved by the Food and Drug Administration (FDA) for patients with PAH to prevent further disease progression.[2] Disease progression is defined as death, prevention of starting intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH. It is the third agent in the endothelin receptor blocker pharmacological class, which includes bosentan (Tracleer®, Actelion) and ambrisentan (Letairis®, Gilead Sciences).

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the two alglucosidase alfa products currently available.[2,3] Alglucosidase alfa serves as an exogenous source of the human enzyme GAA. It is manufactured via recombinant DNA technology in Chinese hamster ovary cells.[4] The only difference between Myozyme® and Lumizyme® is the volume in which these agents are manufactured.[5] Myozyme® is produced in a 160 liter bioreactor, while Lumizyme® is made in a 2000 liter bioreactor. Due to this manufacturing difference, the Food and Drug Administration (FDA) considers the two products biologically different and therefore not interchangeable.

Who should receive Myozyme® as opposed to Lumizyme®? Myozyme® is FDA-approved for any patient with Pompe disease based on open-label trials involving infantile-onset Pompe disease patients.[2] Although late-onset Pompe disease patients may receive this product, it has not been adequately studied in large, controlled clinical trials for safety and efficacy in this population. Lumizyme® is FDA-approved for patients 8 years of age and older with late-onset Pompe disease who do not have evidence of cardiac hypertrophy.[3] Currently, there are no published data from controlled clinical trials evaluating the safety and efficacy of Lumizyme® in infantile-onset patients or in late-onset patients less than 8 years of age. Therefore, these two populations should receive Myozyme®.

What is the recommended dose of alglucosidase alfa and how is it administered? Alglucosidase alfa is administered as a 20 mg/kg intravenous (IV) infusion over a 4 hour period every 2 weeks.[2,3] Utilizing a step-wise rate increase regimen, the entire volume of the infusion is administered through a dedicated line containing an in-line 0.2 µm filter.

What are the side effects and monitoring recommendations for alglucosidase alfa? In open-label trials for Myozyme® involving infantile-onset Pompe disease patients, infusion-associated reactions occurred in 51% of patients.[2] The most common treatment-emergent adverse reactions included fever, diarrhea, rash, vomiting, cough, pneumonia, otitis media, upper respiratory tract infections, gastroenteritis, and decreased oxygen saturation. Additionally, Myozyme® carries a black box warning for anaphylaxis, severe allergic and immune-mediated reactions, and risk of cardiorespiratory failure. Liver enzymes should be evaluated prior to Myozyme® initiation and periodically thereafter due to animal studies showing accumulation of GAA in liver tissue; this accumulation, however, did not result in liver enzyme changes or histopathology. In a randomized, double-blind, placebo-controlled trial for Lumizyme® involving late-onset Pompe disease patients, the most common adverse reactions were infusion reactions.[3] These included but were not limited to anaphylaxis, urticaria, dyspnea, pruritus, and rash/erythema. Similar to Myozyme®, Lumizyme® carries a black box warning for anaphylaxis, severe allergic reactions, and immune-mediated reactions; in addition, it includes a warning about the Risk Evaluation and Mitigation Strategies (REMS) requirements. Periodic urinalysis should be performed in those treated with Lumizyme® due to cases of membranous glomerulonephritis in patients with persistently positive IgG antibodies to alglucosidase. Vital signs should be monitored after each rate increase of an alglucosidase alfa infusion.[2,3] Also, monitoring of IgG antibodies to alglucosidase alfa is recommended every 3 months for 2 years and then yearly. Currently, no commercial tests are available for anti-alglucosidase alfa antibody testing, however, Genzyme provides a testing service.

Are there any restrictions/requirements for obtaining alglucosidase alfa? Lumizyme® is available only through a restricted distribution REMS program called the Lumizyme® ACE (Alglucosidase Alfa Control and Education) program.[6] Prescribers, healthcare facilities, and patients must be enrolled in the program in order to prescribe, dispense, administer, or receive the medication. Each healthcare facility must designate an authorized representative who must complete the REMS program training and certification and enroll the facility. This representative is also responsible for training and keeping track of education provided to all staff who will be involved with ordering, dispensing, and administering Lumizyme®. Additionally, each facility must return a completed Infusion Confirmation Form (ICF) to Genzyme for each patient after every infusion, document the infusion in the patient's medical record using the peel-off sticker from the ICF, maintain records of each patient's enrollment in the REMS program, and re-enroll in the program every year. Myozyme® is not part of a REMS program.

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How macitentan works: Macitentan blocks the binding of endothelin-1 (ET-1) to endothelin receptor A (ET_A) and endothelin receptor B (ET_B). This prevents ET-1 mediated vasoconstriction, fibrosis, proliferation, hypertrophy, and inflammation which can exacerbate PAH. Macitentan was developed by altering the structure of bosentan to increase safety and efficacy.[3,4] Macitentan differs from other endothelin receptor antagonists by having sustained receptor binding and enhanced tissue penetration.[5]

Pharmacokinetics: Macitentan is primarily metabolized via the cytochrome P450 (CYP) enzyme system to its active metabolite, which is accomplished mainly by CYP3A4 and to a lesser extent by CYP2C19.[2] Its active metabolite achieves three times the plasma concentration of macitentan and is believed to contribute 40% of the drug's total pharmacologic activity. The half-life of macitentan and its active metabolite are 16- and 48-hours, respectively, allowing for once daily dosing. The half-life of macitentan is nearly three times longer than bosentan (16- versus 5-hours, respectively) which requires twice daily dosing. However ambrisentan which has a half-life of 9 hours may be given once daily.

Dosing and adverse effects: The recommended dose of macitentan is 10 mg orally taken once daily.[2] The drug may be taken with or without food. There are no adjustments for renal or hepatic impairment. Side effects seen include anemia, nasopharyngitis, upper respiratory tract infections, headache, and elevated liver function tests. Unlike bosentan and ambrisentan, macitentan does not have a warning against use in patients with moderate to severe hepatic impairment.[2,6,7] Like bosentan and ambrisentan, macitentan is classified as a pregnancy-risk category X which means that it is contraindicated in pregnancy.

Drug Interactions: Since macitentan is extensively metabolized through the CYP3A4 system, it can potentially interact with medications that either inhibit or induce this system. Strong CYP3A4 inducers (e.g., rifampin) can decrease the concentration of macitentan in the blood; use of macitentan with strong CYP3A4 inducers should be avoided.[2] Strong inhibitors of CYP3A4 (e.g., ketoconazole) can increase the concentration of macitentan in the blood therefore, the use of macitentan with strong CYP3A4 inhibitors should also be avoided. Unlike bosentan which is an inducer of CYP3A (which includes 3A4 and 3A5) and CYP2C9, macitentan exhibits no relevant inhibitory or inducing effects on those CYP enzymes. In comparison to the other endothelin receptor antagonists, bosentan has the greatest number of drug interactions, whereas ambrisentan is linked to a much lower incidence of documented drug interactions.[6,7]

Risk Evaluation and Mitigation Strategies (REMS) Program: For all females, macitentan is only available through the OPSUMIT® REMS program due to its risk of embryo-fetal toxicity.[2] Significant requirements of this program include:

- Prescribers must be certified with the program by enrolling and completing training
- All patients (males and females) are required to be enrolled following the instructions on the OPSUMIT Patient Enrollment and Consent Form. Male patients are NOT required to complete section 3 of this enrollment form
- Females of reproductive potential must comply with the pregnancy testing and contraception requirements
- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive macitentan

Unlike bosentan, macitentan does not have a REMS requirement for monthly liver function tests.[2,6]

Conclusion: Macitentan is an oral endothelin receptor antagonist that blocks both endothelin receptor A and endothelin receptor B. It is FDA-approved for the treatment of PAH to prevent disease progression. Some advantages over bosentan include once daily dosing, fewer drug-drug interactions, and no REMS requirement for monthly liver function test monitoring. Unlike bosentan and ambrisentan, macitentan does not have a warning against use in patients with moderate to severe hepatic impairment.

References:

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Formulary Update

Additions to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Fluvoxamine immediate-release tablets	SSRI	Treatment of obsessive-compulsive disorder	Doses ≤ 100 mg are recommended to be given at bedtime Doses > 100 mg are recommended to be given twice daily Fluvoxamine controlled-release capsules were not added to the Formulary
Macitentan (Opsumit®)	Endothelin Receptor Antagonist	Treatment of pulmonary arterial hypertension	Restrictions: For initiation of therapy: Restricted to providers from the Respiratory Institute. Prescribers must be registered in the REMS program. For continuation of therapy: The prescriber must be registered in the REMS program, but does not have to be part of the Respiratory Institute.
Riociguat (Adempas®)	sGC Stimulator	Treatment of CTEPH and PAH	Restriction: For continuation of therapy only. The patient must be registered with the Adempas® REMS program under the supervision of a certified prescriber. The inpatient prescriber does not need to be certified for continuation of therapy
Obinutuzumab (Gazyva®)	Antineoplastic Agent	Treatment of chronic lymphocytic leukemia	Restriction: Restricted to Hematology/Oncology for outpatient use only
PrismaSol® BGK 0/2.5	Replacement Solution	Used in CRRT as replacement solution in hemofiltration and hemodiafiltration	Prismasate® will no longer be used for CRRT.
Teduglutide (Gattex®)	GLP-2 analog	Treatment of short bowel syndrome in patients dependent on parenteral nutrition	Restriction: For continuation of home therapy only; provider must be a fellow or staff physician from the Intestinal Transplant Surgical Service.
Melatonin	Dietary Supplement	Treatment of delirium, sleep wake reversal, and insomnia	Melatonin 3 mg tablets will be stocked

CRRT=Continuous renal replacement therapy CTEPH= Chronic thromboembolic pulmonary hypertension
GLP-2=Glucagon-like peptide PAH=Pulmonary arterial hypertension REMS=Risk Evaluation and Mitigation Strategies
sGC=Soluble guanylate cyclase SSRI=Selective serotonin reuptake inhibitor

Formulary Update

Additions to Pediatric CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Alglucosidase alfa (Lumizyme®)	Enzyme	Enzyme replacement therapy for use in patients 8 years of age and older with late onset (non-infantile) Pompe disease without evidence of cardiac hypertrophy	Restriction: Pediatric prescribers and pediatric outpatients need to be enrolled in the Lumizyme® ACE REMS program. Use will also be restricted to infusion sites enrolled in the Lumizyme® ACE REMS program.
Alglucosidase alfa (Myozyme®)	Enzyme	Enzyme replacement therapy for the treatment of infantile-onset Pompe disease	Restriction: For outpatient use only No REMS requirements
Sodium chloride/ aloe vera nasal gel (Ayr® Saline Nasal Gel)	Protectant/ Lubricant	Nasal moisturizing agent	N/A
Melatonin	Dietary Supplement	Treatment of insomnia	Restriction: Child and Adolescent Psychiatry and Cleveland Clinic Children's Hospital for Rehabilitation at the Shaker Campus Melatonin 1– and 3-mg tablets will be stocked.
Pinxav® diaper rash cream	Protectant	Prevention and treatment of diaper rash	N/A
PrismaSol® BGK 0/2.5 PrismaSol® BGK 2/0	Replacement Solution	Used in CRRT as replacement solution in hemofiltration and hemodiafiltration	PrismaSol® BGK 0/2.5 contains 0 mEq/Liter of potassium and 2.5 mEq/Liter of calcium PrismaSol® BGK 2/0 contains 2 mEq/Liter of potassium and 0 mEq/Liter of calcium This calcium-free dialysate will be used for pediatric patients receiving regional citrate anticoagulation.

ACE=Alglucosidase Alfa Control and Education CRRT=Continuous renal replacement therapy N/A=Not applicable
REMS=Risk Evaluation and Mitigation Strategies

Formulary Update

Restriction Changes to Adult CCHS Formulary			
Drug	**Pharmacologic Class**	**Formulary Use**	**Restriction/Comments**
Rituximab (Rituxan®)	Immunosuppressive Agent	For the treatment of cancer and various autoimmune diseases	Restriction change: Staff Physicians from Rheumatology and Nephrology may prescribe for inpatients for acute patient care needs in the hospital (e.g., GPA, Wegener's granulomatosis or MPA). Rituximab should not be ordered and administered to any inpatient due to reasons such as inability to afford co-pay as an outpatient, lack of outpatient insurance coverage, or for patient convenience.

GPA=Granulomatosis with polyangiitis MPA=Microscopic polyangiitis