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From the Department of Pharmacy

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Belimumab: A New Treatment for SLE

By: Janine S. Douglas Pharm.D.

Introduction: Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disorder that affects multiple organ systems.[1,2] It is thought that hyperactivity of B- and T-lymphocytes plays a primary role in the pathogenesis of SLE.[1,3] It is estimated that approximately 1.5 million Americans have some form of lupus.[4] The disease has a higher prevalence in women 15 to 45 years of age and occurs more frequently in African-Americans, Hispanics, Asians, and American Indians.[4] Furthermore, the incidence of SLE is three times higher in African-American than white individuals. Common symptoms of SLE include fever, fatigue, rash, oral ulceration, hair loss, and arthralgias.[4] The disease which can vary in severity is characterized by periods of exacerbations known as flares alternating with asymptomatic intervals of remission. As SLE progresses, major organ systems (e.g., renal, pulmonary, cardiac, central nervous system, hematopoietic) may be impaired resulting in significant morbidity and mortality.[4] There is currently no cure for SLE, so the goal of drug therapy is to prevent and treat flares in order to reduce the risk of SLE-induced organ damage. Standard pharmacotherapy for the treatment of SLE includes the use of nonsteroidal antiinflammatory agents (NSAIDs), antimalarials (e.g., hydroxychloroquine), and glucocorticoids alone or in combination with immunosuppressive medications (e.g., azathioprine, methotrexate, cyclosporine, mycophenolate).[5]

Belimumab (Benlysta®; Human Genome Sciences, Inc. and GlaxoSmithKline) is the first drug approved by the Food and Drug Administration (FDA) for the treatment of SLE in over 50 years.[6] It received FDA-approval in March 2011 for use in adults with active, autoantibody-positive SLE who are concurrently receiving standard therapy.[1,7] Belimumab has not been evaluated in patients with severe lupus nephritis or central nervous system lupus. Additionally, the use of belimumab and combination treatment with biologics and intravenous cyclophosphamide has not been evaluated; therefore, concomitant use is not recommended.[7]

Mechanism of Action: Belimumab, a fully human recombinant monoclonal antibody, blocks the binding of the soluble form of B-lymphocyte stimulator (BLyS), a B-cell survival factor.[5-7] B-lymphocyte stimulator, also known as B-cell activating factor (BAFF), binds to three different receptors: transmembrane activator/calcium-modulator/cyclophilin ligand interactor (TACI), B-cell maturation antigen (BCMA), and BAFF receptor 3 (BR3); this action reduces B-cell apotosis and contributes to the production and differentiation of B-lymphocytes into immunoglobulin-producing plasma cells.[6] Elevated BLyS levels have been directly correlated with increased SLE disease

activity.[5] By inhibiting the biologic activity of BLyS, belimumab has the potential to reduce SLE-related B-cell and related T-cell hyperactivity. In animal studies, BLyS inhibition was associated with clinical improvement of SLE.[3]

Pharmacokinetics: Belimumab pharmacokinetics are linear over a dosage range of 1 to 20 mg/kg.[7] Its volume of distribution is estimated to be 5.29 liters, while its terminal half-life is approximately 19.4 days. Studies in a limited number of patients with renal impairment did not reveal significant differences in pharmacokinetics; therefore, dosage adjustments are not recommended in patients with renal dysfunction. No formal studies have been conducted to determine the effects of hepatic impairment on the pharmacokinetics of belimumab. However, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels have not been found to significantly influence the pharmacokinetic parameters of belimumab. The use of belimumab in patients with severe hepatic impairment has not been evaluated; therefore, no dosage adjustments have been recommended for patients with hepatic insufficiency.

Select Clinical Trials: Wallace and colleagues evaluated the efficacy and safety of belimumab combined with standard of care (SOC) therapy in a phase II, randomized, double-blind, placebo-controlled trial.[8] Patients (n=449) were randomized to receive 1 mg/kg (n=114), 4 mg/kg (n=111), 10 mg/kg (n=111) of intravenous belimumab or placebo (n=113) on days 0, 14, and 28, then every 28 days thereafter for 52 weeks. Enrolled patients needed to meet the American College of Rheumatology (ACR) criteria for SLE with active disease defined by a Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score of ≥4. Other inclusion criteria included history of measurable autoantibodies, stable regimen of prednisone (5 to 40 mg/day), antimalarials, or immunosuppressive agents for at least 60 days prior to first dose. It is important to note that patients did not have to be autoantibody positive at the time of screening. The primary efficacy endpoints were percent change in SELENA-SLEDAI score from baseline to week 24 and time to first mild to moderate flare or severe flare defined by SELENA-SLEDAI Flare Index (SFI) score during 52 weeks. Secondary efficacy endpoints included changes in week 52 of SELENA-SLEDAI, British Isles Lupus Assessment Group (BILAG), Physician's Global Assessment (PGA), and Short Form Physical Component Summary 36 (SF-36 PCS) scores, time to first SLE flare during and after 24 weeks, and percent of patients with prednisone dose reduction ≤ 7.5 mg/day or 50% reduction from baseline to weeks 40 to 52. There were no significant differences in SELENA-SLEDAI scores from baseline to week 24 among the three belimumab treatment groups and the placebo group. Furthermore, there were no significant differences in time to first flare as defined by SFI over 52 weeks between combined belimumab treatment and placebo groups. In addition, there were no significant differences in prednisone dose reductions or BILAG scores. However, the median time to flare between week 24 to 52 was 154 days in the combined belimumab group compared to 108 days in the placebo group and was statistically significant (p=0.0361). There were also significant differences in mean changes in PGA scores in the combined belimumab group compared with the placebo group (p=0.0019) by week 52. Additionally, there was significant improvement in the SF-36 PCS scores in the belimumab 10 mg/kg group compared to placebo (p=0.0167). In a subgroup analysis of serologically active patients, there were significantly greater reductions in SELENA-SLEDAI scores from baseline to week 52 in patients treated with belimumab versus the placebo group (p=0.0435). Furthermore, significant improvements were also seen in PGA (p=0.0011) and SF-36 PCS (p=0.041) scores in the belimumab treatment arms compared with the placebo arm. Although the incidence of most adverse effects was similar between treatment and placebo groups, more cases of urticaria, serious infections (e.g., pneumonia, cellulitis) and infusion-related reactions were reported in belimumab-treated patients. The authors concluded that patients who had serologically active SLE demonstrated a better response to belimumab therapy with SOC compared to SOC alone and that the drug was generally well tolerated.

Navarra and associates evaluated the efficacy and safety of belimumab in patients with active SLE in a 52 week phase III, randomized, placebo-controlled trial known as BLISS-52.[9] This study included adult patients (n=865) who were randomized to receive intravenous belimumab 1 mg/kg (n=288), 10 mg/kg (n=290), or placebo (n=287) on days 0, 14, 28, and then every 28 days until 48 weeks with SOC therapy. Patients with active disease with a positive ANA titer (titer ≥1:80) or anti-dsDNA antibody level (≥30 IU/mL) who met ACR criteria and were receiving a stable treatment regimen of prednisone (0 to 40 mg/day) or antiinflammatory, antimalarial, or immunosuppressive drugs for at least 30 days prior to first dose were included. Patients were enrolled from centers in Latin America, Asia, Australia, and eastern Europe. The primary efficacy endpoint was the response rate at week 52 assessed by Systemic Lupus Erythematosus Responder Index (SRI). A significant SRI response was defined by the following criteria: reduction of at least 4 points in the SELENA-SLEDAI score, no new BILAG A organ domain score, no more than one new BILAG B organ domain score, and no worsening in PGA score at week 52 compared to baseline. Some secondary endpoints included the percentage of patients with at least a 4 point reduction in SELENA-SLEDAI score at week 52, mean change in PGA score at week 24, mean change in the SF-36 PCS score at week 24, and percentage of patients with at least an average 25% reduction in prednisone dose from baseline to 7.5 mg/day or less during weeks 40 to 52. A significant improvement in SRI response rates at week 52 occurred for both

the belimumab 1- and 10-mg/kg groups compared to placebo (p=0.0129 and p=0.0006, respectively). Furthermore, there was a significant improvement in SELENA-SLEDAI scores for patients in both the belimumab 1- and 10-mg/kg treatment groups compared to placebo (p=0.0189 and p=0.0024, respectively). However a significant reduction in the PGA score at week 24 occurred only in the 10 mg/kg belimumab group compared with placebo (p=0.0003). No significant differences in SF-36 PCS scores between belimumab treatment groups compared to placebo were observed at week 24. Steroid sparing activity as previously defined was found to be statistically significant in only the 1 mg/kg belimumab group compared with the placebo group (p=0.0252). The number of severe hypersensitivity or infusion reactions was greater in the belimumab groups than the placebo group. No serious infections associated with severe neutropenia or hypogammaglobulinemia were reported. The authors concluded that belimumab represented a new targeted therapy which could potentially improve the quality of life for SLE patients.

Preliminary results from a 76-week randomized, double-blind placebo-controlled phase III study known as BLISS-76 have been released.[6,7,10] This trial evaluated the safety and efficacy of belimumab in seropositive SLE patients (n=819) who met the following inclusion criteria: ANA ≥1:80 and/or anti-dsDNA ≥ 30 IU/mL, SELENA-SLEDAI score ≥6 , and stable SOC therapy for ≥ 30 days. Patients were randomized to receive belimumab 1 mg/kg (n=271) or 10 mg/kg (n=273) plus SOC therapy versus placebo (n=275) plus SOC on days 0, 14, 28, and every 28 days thereafter for 72 weeks. The primary endpoint was the SRI response at 52 weeks. Secondary endpoints included assessment of SELENA-SLEDAI, BILAG, and SFI scores. There was a significant difference in the SRI response rate in the 10 mg/kg belimumab group compared to placebo at 52 weeks (p=0.0021); the SRI response rate for the 1 mg/kg treatment group was not significantly different from placebo. There was a significant reduction in SELENA-SLEDAI scores in only the 10 mg/kg group compared with the placebo group (p=0.006). No significant differences in BILAG or average SFI scores were noted. However, the severe SFI score for patients in the belimumab 1 mg/kg group was significantly better than for those patients in the placebo group (p=0.023). Overall adverse reactions were comparable between the belimumab and placebo groups, however serious infusion reactions were more prevalent in the belimumab groups. The authors concluded that belimumab significantly improved SRI response rates in seropositive SLE patients with minimal adverse effects.

Adverse Reactions: The most common adverse effects reported in placebo-controlled clinical trials with belimumab 10 mg/kg therapy occurring in ≥3% of patients include nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremities, depression, migraine, pharyngitis, cystitis, leukopenia, and viral gastroenteritis. The most common adverse reactions that resulted in discontinuation of therapy included infusion reactions, infections, and lupus nephritis.[7] Treatment with belimumab has also been associated with mortality, serious infections, malignancy, depression, hypersensitivity reactions including anaphylaxis, and infusion reactions. During three placebo-controlled clinical trials, more deaths were reported in the belimumab treatment groups than the placebo groups (11 versus 3, respectively). Causes of death included infection, cardiovascular disease, and suicide. It is recommended that patients who are being treated for chronic infections not receive belimumab and those who develop infections while receiving belimumab have their therapy temporarily discontinued. Most patients who experienced serious depression or suicidal behavior while on belimumab therapy had a prior psychiatric history and were receiving psychoactive medications. The use of premedication may reduce the incidence and severity of hypersensitivity and infusion reactions; however, the evidence to support the efficacy of premedication is inconclusive. In clinical trials, anti-belimumab antibodies were detected in 4 of 563 patients receiving belimumab 10 mg/kg and 27 of 559 patients receiving belimumab 1 mg/kg. The exact clinical significance of anti-belimumab antibody development is unknown at this time.

Reduced Clinical Effect in Black/African-American Patients: A subgroup analysis utilizing data from the BLISS-52 and BLISS-76 trials found that the SRI response rates in Black/African-American SLE patients treated with belimumab were lower than in Black/African-American SLE patients treated with placebo.[7] However, the number of Black/African-American SLE study participants was relatively small (4% in the BLISS-52 and 14% in BLISS-76). Therefore, further investigations are needed to determine if belimumab is effective in that specific population. In the meantime, the manufacturer recommends that this drug be used with caution in Black/African-American patients.

Drug Interactions: Belimumab has not been formally evaluated in drug interaction studies.[5] However, in clinical trials, concomitant use of immunomodulatory and immunosuppressant agents (e.g., azathioprine, methotrexate, mycophenolate), antimalarials, HMG-CoA reductase inhibitors (statins), corticosteroids, angiotensin pathway antihypertensives, and NSAIDs did not have an effect on belimumab's pharmacokinetic parameters. Belimumab's effect on the pharmacokinetics of other medications has not been determined. Live vaccines should not be administered 30 days prior to or concurrently with belimumab treatment, since clinical safety of this combination has not been established. It is possible that belimumab may interfere with the immune response to immunizations.

Pregnancy and Lactation: Belimumab is classified as pregnancy-risk category C due to the lack of adequate and well-controlled trials in pregnant women.[7] Additionally, immunoglobulins and belimumab can cross the placenta. The use of belimumab in pregnancy should only occur when the potential maternal benefit outweighs the risk to the fetus. Women of childbearing age should use adequate measures to prevent pregnancy while on belimumab and for at least 4 months after the final treatment. A pregnancy registry has been established for patients who become pregnant while taking belimumab. Patients and healthcare professionals are encouraged to call 1-877-681-6296 to enroll in the pregnancy registry. It is unknown whether belimumab is excreted in human breast milk or systemically absorbed after ingestion. Since maternal antibodies are excreted in breast milk, the manufacturer recommends that lactating mothers either discontinue breastfeeding or discontinue the drug.

Dose and Administration: The recommended dose of belimumab is 10 mg/kg every 2 weeks for the first three doses, and then every 4 weeks thereafter.[5] Belimumab should be reconstituted only with sterile water for injection; the reconstituted solution should be further diluted in 250 mL of sodium chloride 0.9%. The drug is incompatible with intravenous dextrose solutions. No intravenous drug compatibility studies have been performed with belimumab; therefore, it is recommended that the drug be administered through a dedicated line. Belimumab intravenous infusion should be infused over 1 hour. Prior to administering belimumab, patients should be premedicated to prevent infusion and/or hypersensitivity reactions. Patients should be closely monitored for infusion-related reactions. If an infusion reaction develops, the administration rate may be decreased or interrupted; however, the drug should be immediately discontinued if a serious hypersensitivity reaction (e.g., anaphylaxis) occurs.

Risk Evaluation and Mitigation Strategy: Belimumab is not associated with a Risk Evaluation and Mitigation Strategy (REMS) program. However, a medication guide is required to be distributed with the first administration of belimumab by a healthcare professional to a patient in an outpatient setting such as an infusion center.[7,11] If a healthcare professional administers belimumab while the patient is hospitalized, distribution of the medication guide is not required.[11]

Cost and Formulary Status: Belimumab is available as a lyophilized powder in single-use 5-mL vials containing 120 mg and single-use 20-mL vials containing 400 mg. The average wholesale price (AWP) is $531 for the 5-mL single-use vial and $1772 for the 20-mL single-use vial. Belimumab was added to the CCHS Formulary in June 2011; its use is restricted to Rheumatologists that practice within CCHS for outpatient use only.

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Formulary Update

The CCHS Medical Staff Pharmacy and Therapeutics Committee met on June 28, 2011, and the Cleveland Clinic Local Pharmacy and Therapeutics Committee met on July 11, 2011. The following decisions were made:

Adults:

Formulary Additions:

Antimicrobial:

1. **All HIV antiretrovirals agents:** All of these agents may not be stocked in the pharmacy, but they are considered Formulary. If a patient comes in from home on one of these medications, then the drug needs to be obtained in order to prevent interruptions or delays in patient therapy which can be detrimental to the patient and lead to viral resistance.
2. **Acyclovir (Zovirax®) and valacyclovir (Valtrex®)**: Acyclovir and valacyclovir are now the preferred herpes simplex virus (HSV) antivirals on the CCHS Formulary. However, famciclovir will be available for use on a non-formulary basis for continuation of home therapy in select transplant patients.
3. **Levofloxacin (Levaquin®):** Generic levofloxacin will replace moxifloxacin. At Main Campus, levofloxacin will replace moxifloxacin for the treatment of community-acquired pneumonia (CAP) in beta-lactam allergic patients. Ciprofloxacin will remain the preferred Formulary quinolone for treatment of gram-negative and nosocomial infections. This conversion from moxifloxacin to generic levofloxacin will take place on Tuesday, August 16th.

Hematology/Oncology:

1. **Ipilimumab (Yervoy®):** It is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody that is FDA-approved for the treatment of unresectable or metastatic melanoma. Ipilimumab carries a black box warning for severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. Ipilimumab is available for use now.
    a. Ipilimumab is **restricted** to the Department of Hematology and Medical Oncology for **outpatient use only** using its FDA-approved dosing (3 mg/kg every 3 weeks x 4 doses).
2. **Abiraterone (Zytiga™):** It is a CYP17 inhibitor indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel. Abiraterone is administered as 1000 mg orally daily in combination with prednisone 5 mg given twice daily. Abiraterone must be taken on an empty stomach. Exposure (area under the curve) of abiraterone increases up to 10-fold when abiraterone is taken with meals. Therefore, abiraterone should be given at least 1 hour before or 2 hours after a meal. It is restricted to continuation of therapy from home.
3. **Eltrombopag (Promacta™):** It is a thrombopoietin receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Eltrombopag carries a black box warning regarding the risk for hepatotoxicity. The usual starting dose is 50 mg orally daily. For patients with Asian ancestry or in moderate or severe hepatic insufficiency, a lower dose, 25 mg daily, should be used. Eltrombopag should be administered on an empty stomach (1 hour before or 2 hours after a meal), and there should be a 4-hour interval between the administration of eltrombopag and other medications, foods, or supplements containing polyvalent cations (e.g., iron, calcium, aluminum, magnesium, selenium, and zinc). Eltrombopag has a REMS program called Promacta® Cares™. Patients, prescribers, and pharmacies must be enrolled in the program. The Taussig Outpatient Pharmacy and the Inpatient Pharmacy are registered to dispense eltrombopag.
    a. Eltrombopag is **restricted** to the Department of Hematology and Medical Oncology.
4. **Pegylated interferon alfa-2b (Sylatron™):** It is an alpha interferon indicated for the adjuvant treatment of melanoma with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy. The drug carries a black box warning regarding the risk for depression and other neuropsychiatric disorders. The usual dose is 6 mcg/kg/week subcutaneously for 8 doses, followed by 3 mcg/kg/week subcutaneously for up to 5 years. Acetaminophen can be administered as premedication in doses of 500 to 1000 mg orally 30 minutes prior to the first dose and as needed for subsequent doses.
    a. Pegylated interferon alfa-2b is **restricted** to the Department of Hematology and Medical Oncology for **outpatient use only**.

Neurosciences:

1. **Lamotrigine extended-release (Lamictal XR®)**: Immediate-release (IR) lamotrigine is currently on Formulary at the Main Campus. Lamictal XR® is approved for adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures and partial onset seizures, with or without secondary generalization in patients 13 years of age or older. Compared to lamotrigine IR, Lamictal XR® plasma levels are characterized by lower peaks, longer time to peak concentration, and less peak-to-trough fluctuations. Lamictal XR® is not considered bioequivalent to lamotrigine IR. There is a recommended escalation and maintenance dosing for PGTC and partial-onset seizures based on concomitant medications. Titration is recommended to reduce the potential for rash.

Critical Care/ Pulmonary:

1. **Tadalafil (Adcirca®)**: It is a phosphodiesterase 5 (PDE5) inhibitor indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability. The usual dose is 40 mg (two 20-mg tablets) once daily, with or without food. Dividing the dose (40 mg) over the course of the day is not recommended. Sildenafil (Revatio®), another phosphodiesterase-5 (PDE5) inhibitor, will remain on the Formulary with no restrictions.
    a. Tadalafil is **restricted** to use in pulmonary hypertension patients.
2. **Ambrisentan (Letairis®)**: It is an endothelin receptor antagonist indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and delay clinical worsening. Treatment with ambrisentan is initiated at 5 mg orally once daily with or without food, and can be increased to 10 mg once daily if 5 mg is tolerated. Women of childbearing potential should only be treated after a negative pregnancy test and only in women who are using two acceptable methods of contraception unless the patient has had a tubal sterilization or chooses to use a Copper T 380A Intrauterine Device (IUD) or LNg 20 Intrauterine System (IUS), in which case no additional contraception is needed. Monthly pregnancy tests should be obtained. Because of the risk of birth defects if used during pregnancy, ambrisentan carries a black box warning and access is restricted as part of the REMS LEAP (LETAIRIS Education and Access Program). Risk of hepatic injury was removed from the boxed warning for ambrisentan and routine monitoring of hepatic enzymes is no longer required as of March 2011.
    a. Ambrisentan is **restricted** to physicians within the Respiratory Institute for initiation of therapy and the prescriber must be registered with the LEAP Program. For continuation of therapy, prescribers must also must be registered with the LEAP Program, but do not have to be part of the Respiratory Institute. Please see the Letairis® website for prescriber and patient enrollment forms, roles, and responsibilities of the LEAP Program: http://www.letairisrems.com/REMS_Program.aspx
3. **Treprostinil for inhalation (Tyvaso®)**: It is a prostacyclin vasodilator indicated for the treatment of PAH (WHO Group 1) to improve exercise ability. The initial dose is 18 mcg (or 3 inhalations) every 4 hours, 4 times/day, decreased to 1 to 2 inhalations if not tolerated, then increased to 3 inhalations as tolerated. Inhaled treprostinil should be titrated to a target maintenance dosage of 9 breaths or 54 mcg per treatment session as tolerated. Administration is only by the Tyvaso™ Inhalational System. Treprostinil (Remodulin®) is available for subcutaneous or intravenous administration and will remain on the Formulary with restrictions to the Pulmonary Hypertension Committee.
    a. Trepoprostinil for inhalation is **restricted** to physicians within the Respiratory Institute for initiation of therapy. Any prescriber may continue treprostinil for inhalation therapy from home.
4. **Mannitol inhalation powder (Aridol®)**: Mannitol is a sugar alcohol indicated for the assessment of bronchial hyperresponsiveness in patients 6 years of age or older who do not have clinically apparent asthma, as part of a physician's overall assessment of asthma. Mannitol inhalation powder has a black box warning for bronchoconstriction and severe bronchospasm and should only be used under the direction of a trained medical professional and for diagnostic purposes only. The drug is contraindicated in patients with known hypersensitivity to mannitol or to the gelatin used to make the capsules. The Pulmonary Function Laboratories at Cleveland Clinic intend to use both methacoline and/or mannitol inhalation powder for the diagnosis of asthma in selected patients.
    a. Mannitol inhalation powder is **restricted** to the Pulmonary Function Laboratories.

Internal Medicine:

1. **Belimumab (Benlysta®)**: It is a B-lymphocyte stimulator (BLyS)-specific inhibitor indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. Belimumab has not been assessed in patients with severe active lupus nephritis or severe active central nervous system lupus, or in combination with other biologics or intravenous cyclophosphamide. Belimumab is dosed 10 mg/kg at 2-week intervals for the first 3 doses and at 4-week intervals thereafter. Premedication for prophylaxis against infusion reactions and hypersensitivity reactions can be considered.
    a. Belimumab is **restricted** to Rheumatologists that practice within CCHS for **outpatient use only**.

Internal Medicine:

2. **Pegloticase (Krystexxa®)**: It is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients refractory to conventional therapy. Pegloticase carries a black box warning due to the risk of anaphylaxis and infusion reactions. Therefore, pegloticase should be administered in healthcare settings and by healthcare providers prepared to manage anaphylaxis and infusion reactions and patients should be pre-medicated with antihistamines and corticosteroids. The recommended dose of pegloticase is 8 mg IV infusion every 2 weeks.
    a. Pegloticase is **restricted** to Rheumatologists that practice within CCHS for **outpatient use only**.
3. **Intravenous Iron:** The inpatient intravenous iron product on the CCHS Formulary is sodium ferric gluconate complex (Ferrlecit®) and the outpatient intravenous iron product on the CCHS Formulary is iron sucrose (Venofer®). Iron sucrose and sodium ferric gluconate are equally efficacious, but iron sucrose is advantageous in the outpatient setting with its ease of administration (i.e., fewer injections) and better reimbursement; however, for the inpatient setting sodium ferric gluconate is advantageous due to lower contract pricing. Iron dextran will remain on the Formulary and can be administered either in the inpatient or outpatient setting. Ferumoxytol (Feraheme®) remains non-formulary (not stocked).

Cardiology:

1. **Ranolazine (Ranexa®):** It is indicated for the treatment of chronic angina and exerts anti-anginal and anti-ischemic effects without changing hemodynamic parameters (e.g., heart rate or blood pressure). Ranolazine is a substrate and inhibitor of CYP3A4, CYP2D6, and P-glycoprotein. While there are multiple important drug interactions with ranolazine, the Committee approved that if a patient is ordered simvastatin and ranolazine concurrently, the simvastatin dose should be reduced to no more than 20 mg daily (as ranolazine may increase the serum concentration of simvastatin 2-fold). The Committee also approved if a patient is ordered atorvastatin and ranolazine concurrently, the atorvastatin dose should be reduced to no more than 40 mg daily (P-glycoprotein substrate level may be increased by P-glycoprotein inhibitors). Pharmacists cannot automatically make the dosage adjustments; the prescriber must be contacted to obtain permission to make the dosage adjustments and the discussion must be documented in an I-Vent.

Transplant:

1. **Generic tacrolimus:** The inpatient pharmacy will convert from brand tacrolimus (Prograf®) to generic tacrolimus. The inpatient pharmacy and the Cleveland Clinic ambulatory pharmacies will carry one brand of generic tacrolimus (i.e., the same manufacturer). The specific conversion date will be announced at a later time (most likely October).
2. Tacrolimus powder will now be used to compound tacrolimus oral suspension in the pharmacy instead of emptying the powder from the commercially available capsules. This practice change will result in less waste and more accurate dosing of tacrolimus for patients requiring an oral suspension.

Adults:

Not Added to the CCHS Formulary:

1. **Ceftaroline (Teflaro™)** will not be added to the formulary due to the limited (if any) added benefit to the current Formulary antimicrobials at this time.
2. **Ramelteon (Rozerem®)** was previously reviewed in 2006 for use at the Main Campus, and it was approved for use with restrictions for use in the Departments of Psychiatry, Neurology, and Pulmonary Medicine. Ramelteon is indicated for the treatment of insomnia characterized by difficulty with sleep onset. Due to low use and lack of definitive advantage over other agents, ramelteon will be deleted from the Formulary.
3. **Tranexamic acid tablets (Lysteda®)** will not be added to the Formulary due to lack of therapeutic need for this drug.

Adults:

Restriction Change:

1. Intravenous immune globulin (IVIG) will not be dispensed for patients with *C. difficile* unless the patient also has hypogammaglobulinemia. Hypogammaglobulinemia can generally be defined as an IgG level less than 400 mg/dL.
2. IVIG use is approved for the lung transplant protocol for antibody-mediated rejection (AMR) and desensitization. The lung transplant protocol for AMR and desensitization uses higher doses than the recommended 2 g/kg total dose. The IVIG dosing recommendations for the lung transplant protocol are as follows: IVIG 1 g/kg (dose based on IBW or AdjBW) for 3 doses for mild to moderate AMR and for 5 doses in severe cases of AMR.

Adults:

Therapeutic Interchange:

There will be an addition to the existing inpatient 5HT3-Receptor Antagonist Chemotherapy-Induced Nausea and Vomiting (CINV) therapeutic interchange:

Currently, for inpatient CINV treatment, oral or IV dolasetron (Anzemet®) or granisetron (Kytril®) are converted to generic ondansetron. Now, palonosetron (Aloxi®) 0.25 mg IV will also be automatically converted to ondansetron 8 mg IV for the inpatient setting only. Inpatients undergoing the Carboplatin Desensitization Protocol as written by Gynecologic Oncology Staff Physicians and outpatients may continue to receive palonosetron.

Children's Hospital/Pediatrics:

Additions to the CCHS Pediatric Formulary:

Antimicrobial Agents:

1. **All HIV antiretrovirals agents.**
    a. All of these agents may not be stocked in the pharmacy, but they are considered formulary. If a patient comes in on one of these medications from home, the drug needs to be obtained to not cause interruptions or delays in patient therapy which can be detrimental to the patient and lead to viral resistance.
2. **Acyclovir (Zovirax®) and valacyclovir (Valtrex®)**: Acyclovir and valacyclovir are now the preferred herpes simplex virus (HSV) antivirals on the CCHS Formulary. However, famciclovir will be available for use on a non-formulary basis for continuation of home therapy in select transplant patients.
3. **Levofloxacin (Levaquin®):** Generic levofloxacin will replace moxifloxacin. At Main Campus, levofloxacin will replace moxifloxacin for the treatment of community-acquired pneumonia (CAP) in beta-lactam allergic patients. Ciprofloxacin will remain the preferred Formulary quinolone for treatment of gram-negative and nosocomial infections.

Gastrointestinal/ Nutrition Agents:

1. **Cholecalciferol (D-Visol®)**: It is a 400 units/mL vitamin D3 supplement that is gluten-free, sugar-free, and citrus flavored and will be the preferred vitamin D supplement due to lower cost; however, ergocalciferol (Drisdol®) 8000 units/mL will remain on the Formulary and will be reserved for use in larger children.
2. **Glycopyrrolate oral solution (Cuvposa®)**: Previously, pharmacy has compounded an oral glycopyrrolate solution from the commercially available injectable solution. Since a 1 mg/ 5mL oral solution is commercially available, pharmacy will no longer be making the compounded glycopyrrolate oral solution. The benefits of using the commercially available glycopyrrolate oral solution include decreased risk for compounding errors and increased convenience for patients needing the product on an outpatient basis.

Hematology/Oncology

1. **Palifermin (Kepivance®):** It is a recombinant human keratinocyte growth factor that increases epithelial thickening in the squamous epithelium of the oral cavity and increases crypt depth and villus height of the small intestine. Palifermin is FDA-approved in adults for decreasing the incidence and duration of severe oral mucositis in patients receiving myelotoxic therapy requiring hematopoietic stem cell support. It is not FDA-approved in children, but many institutions are currently using this product in high-risk patients. Dosing for this agent will be the same as what is used for adults: 60 mcg/kg/day administered as an IV bolus for 3 consecutive days.
    a. Palifermin is **restricted** to pediatric bone marrow transplant patients meeting the following criteria: Risk for Grade IV mucositis, or airway compromise due to severe mucositis following hematopoietic stem cell transplant (HSCT):
        i. Patients (0-18 years) with hematological malignancy who are undergoing total-body irradiation (TBI) + (cytoxan or etoposide) based conditioning if they have evidence of previous oral mucositis $\geq$ Grade III
        ii. Toddlers (age $\leq$ 3 years) who are undergoing conditioning therapy for autologous transplant for either HR-NB or brain tumor
        iii. Infants (age $\leq$ 12 months) who are undergoing allogenic transplant for any disorder that requires myeloablative treatment
2. **Magnesium amino acid chelate tablets:** This formulation may provide better absorption and less diarrhea than other forms of magnesium supplementation. Only the Nature's Blend product should be carried since this manufacturer has been granted a good manufacturing practice (GMP) certificate. Each capsule contains magnesium elemental 300 mg (from magnesium oxide and magnesium amino acid chelate) and the product contains no gluten or preservatives.
    a. Magnesium amino acid chelate tablets are **restricted** to pediatric bone marrow transplant patients
3. **Nelarabine (Arranon®):** It is a water soluble prodrug of 9-b-d-arabinofuranosylguanine (ara-G). Ara-G is a deoxyguanosine derivative with greater toxicity to T lymphoblasts than deoxyguanosine. Nelarabine is FDA-approved for use in pediatric patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) who have previously failed or relapsed following treatment with two other chemotherapy regimens. Patients who are enrolled in ongoing Children's Oncology Group (COG) trials may receive nelarabine without having failed other therapies. The FDA-approved pediatric dosing regimen is 650 mg/m^2 intravenously over 1 hour on days 1 through 5 and this may be repeated every 21 days.
    a. Nelarabine is **restricted** to the Department of Hematology/Oncology.

Neurology:

1. **Fluphenazine decanoate (Prolixin®)**: It is a long-acting injectable antipsychotic agent, which is infrequently used in the inpatient setting due to short length of stay.
    a. Fluphenazine decanoate is **restricted** to Child and Adolescent Psychiatry.
2. **Haloperidol decanoate (Haldol®):** It is a long-acting injectable antipsychotic agent, which is infrequently used in the inpatient setting due to short length of stay.
    a. Haloperidol decanoate is **restricted** to Child and Adolescent Psychiatry.
3. **Lisdexamphetamine (Vyvanse®):** It is a schedule II controlled substance that is FDA-approved for the treatment of attention deficit hyperactivity disorder (ADHD) in children > 6 years of age. It is thought to work by inhibiting the reuptake of dopamine and norepinephrine into presynaptic neurons, thus increasing the availability of these neurotransmitters in the extraneuronal space. Dosing is 30 mg once daily in the morning. This can be adjusted by 10 or 20 mg weekly to a maximum of 70 mg daily. Lisdexamphetamine is available as a capsule that may be swallowed whole or it can be opened and dissolved in water with the resulting solution consumed immediately.
4. **Dexmethylphenidate (Focalin® and Focalin® XR):** It is a schedule II controlled substance that is FDA-approved for the management of attention deficit hyperactivity disorder (ADHD) in children > 6 years of age. Dexmethylphenidate is the more pharmacologically active enantiomer of methylphenidate and the mechanism of action is the same as lisdexamphetamine.
    a. Initiation of dexmethylphenidate therapy is **restricted** to Child and Adolescent Psychiatry; however any prescriber may continue home therapy.

Neurology:

5. **OnabotulinumtoxinA (Botox®):** It is a neurotoxin used for its neuromuscular blocking effects for various indications in adult patients. Although not FDA-approved for treating spasticity and dystonias in conjunction with physical and occupational therapy in pediatric patients, there have been numerous randomized, controlled trials that have shown beneficial effects in both lower and upper limb spasticity in pediatric patients with cerebral palsy. Dosing and frequency of dosing will vary from patient to patient.
    a. OnabotulinumtoxinA is **restricted** to the Departments of Pediatric Neurology, Psychiatry, and Ears, Nose, and Throat (ENT) for **outpatient** treatment of spasticity, dystonias, and drooling.

Rheumatology:

1. **Tocilizumab (Actemra®):** It is an interleukin 6 (IL-6) receptor inhibiting antibody that is FDA-approved for children > 2 years of age with juvenile idiopathic arthritis (JIA). It may be used alone or in combination with methotrexate or other disease-modifying antirheumatic drugs (DMARDS). It has been proven to reduce steroid dependency in patients with JIA which leads to a decrease in steroid related adverse events. This agent carries a black box warning regarding the risk of serious infections.
    a. Tocilizumab is **restricted** to the Department of Rheumatology for treatment of **outpatients** refractory to other therapies.

Not Added to the CCHS Pediatric Formulary:

1. **Intravenous (IV) acetaminophen (Ofirmev®):** It should not be ordered, stocked, or dispensed.

Therapeutic Interchange:

Proton Pump Inhibitors (PPIs)

Oral and injectable formulations of pantoprazole (Protonix®) are the PPIs on Formulary for adult patients. Oral formulations of pantoprazole are FDA-approved in patients ≥ 5 years of age; the injectable formulation does not have an approved pediatric indication. There are other oral proton pump inhibitors on the market that are FDA-approved for lower age ranges compared to that of pantoprazole, and IV esomeprazole is FDA-approved for patients as young as 1 month of age. Therefore, for CCHS pediatric patients:

1. Pediatric patients requiring an oral PPI formulation:
    a. All patients unable to swallow solid dosage forms will be converted to compounded lansoprazole (Prevacid®) oral suspension or lansoprazole orally-disintegrating tablets (Prevacid® SoluTabs)
    b. Patients < 5 years of age will be converted to compounded lansoprazole (Prevacid®) oral suspension or lansoprazole orally-disintegrating tablets (Prevacid® SoluTabs)
    c. Patients ≥ 5 years of age able to swallow solid dosage forms will be converted to pantoprazole tablets
2. Pediatric patients requiring an injectable PPI formulation will be converted to IV esomeprazole (IV Nexium®). This interchange will begin Tuesday, August 23rd.