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Pharmacotherapy Update

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Roflumilast: A New Oral, Once-Daily Therapy for COPD

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Introduction: Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation that is not fully reversible with symptoms including cough, sputum production, and dyspnea on exertion.[1] The World Health Organization (WHO) estimates approximately 64 million people worldwide are affected by this condition with its prevalence and mortality increasing significantly over the past 2 decades.[2] Risk factors for development of COPD include: environmental exposure to tobacco smoke or air pollution, occupational exposure to dust and chemicals, genetic predisposition, airway hyperresponsiveness, and impaired lung growth.[1,3] The WHO has projected that COPD will be the third leading cause of death by 2030.[2] The selective phosphodiesterase-4 (PDE4) inhibitor, roflumilast (Daliresp®; Forest Pharmaceuticals) was approved by the United States Food and Drug Administration (FDA) on February 28, 2011.[4] Roflumilast is indicated as a treatment to decrease the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[5]

COPD Review: Airflow limitation in patients with COPD is typically progressive and associated with an intense inflammatory response within the lungs to noxious particles or gases.[1,3] This inflammatory process not only involves the airways, but also the pulmonary vasculature and lung parenchyma. Neutrophils, macrophages, and CD8+ lymphocytes release proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL-8), and leukotriene (LT) B_4. Additionally, oxidative stress and an imbalance between proteases and antiproteases play a major role in the ongoing pulmonary hyperactivity sequence.[1]

A diagnosis of COPD should be kept in mind in patients who have a history of exposure to risk factors as well as complaints of dyspnea, chronic cough, or sputum production. These key indicators along with spirometry confirm the diagnosis of COPD.[3] Patients with COPD have a forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) ratio of less than 70% and a reduction in FEV_1 percent predicted. In order to standardize care for patients with COPD, the National Heart, Lung, and Blood Institute and the WHO introduced the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines in 2001. The GOLD Guidelines which are presented in Figure 1 classify COPD according to spirometry and symptoms.

Short-acting bronchodilators are recommended as needed for all stages of COPD and include $beta_2$-agonists such as levalbuterol (Xopenex®), albuterol (e.g., Proventil®), terbutaline, and anticholinergic agents such as ipratropium (Atrovent®).[3] Long-acting bronchodilators, which are usually intiated in Stage II COPD, include

beta$_2$-agonists such as formoterol (e.g., Foradil®), salmeterol (Serevent®), or indacaterol (Arcapla™), and anticholinergic agents such as tiotropium (Spiriva®); these agents are more effective than short-acting bronchodilators when used regularly, but are not indicated for acute symptomatic relief. Additionally, combining bronchodilators from different classes has been shown to be more effective than increasing the dose of one agent alone. Although regular use of inhaled corticosteroids initiated in Stage III COPD does not modify the long-term decline in FEV_1, therapy may improve health status and reduce the frequency of exacerbations in patients with FEV_1<50% predicted who are symptomatic. However, the long-term safety and efficacy of inhaled corticosteroids are unknown. Inhaled corticosteroid products include beclomethasone (QVAR®), budesonide (Pulmicort®), and fluticasone (Flovent®). Combination corticosteroid products with long-acting beta$_2$-agonists include formoterol/budesonide (Symbicort®) and salmeterol/fluticasone (Advair®). Combination products may increase patient compliance and reduce the number of inhalations needed per day. Patients with Stage IV COPD have a very poor quality of life with potentially fatal exacerbations. Current GOLD guidelines recommend long-term oxygen therapy for patients with chronic respiratory failure and consideration of surgical treatments.

Figure 1: GOLD Guidelines[3]

COPD Classification and Therapy Recommendations				
Spirometry Measurement	**Mild Stage I**	**Moderate Stage II**	**Severe Stage III**	**Very Severe Stage IV**
FEV_1/FVC	<0.7	<0.7	<0.7	<0.7
FEV_1 % predicted	≥80%	50% - 80%	30% - 50%	<30% or <50% plus chronic respiratory failure
Active reduction of risk factors + influenza vaccine ----------> *Add*: Short-acting bronchodilator as needed ---------->				
		Add: Regular use of one or more long-acting bronchodilators and rehabilitation (when needed)		
			Add: Inhaled corticosteroids if repeated exacerbations	
				Add: Long-term oxygen if chronic respiratory failure *Consider:* Surgery

GOLD=Global Initiative for Chronic Obstructive Lung Disease COPD=Chronic Obstructive Pulmonary Disease
FEV_1 =Forced Expiratory Volume in One Second FEV_1/FVC=Forced Expiratory Volume in One Second/Forced Vital Capacity

Mechanism of Action: Methylxanthines (e.g., theophylline) were historically considered first-line therapy for COPD.[1] These agents produce bronchodilation through a variety of mechanisms including inhibition of phosphodiesterase (PDE) which raises intracellular cyclic adenosine monophosphate (cAMP) levels.[6] Increases in cAMP have an inhibitory effect on various inflammatory and immunomodulatory cells.[7] Therefore, PDE inhibition is believed to be an important factor in reducing the chronic inflammation associated with COPD. There are at least eleven isoenzymes of PDE that vary in distribution among different tissues and cell types in the body.[8] The isoenzyme subtype PDE4 is highly expressed in airway inflammatory cells involved in the pathogenesis of COPD.[7,8] Theophylline, a non-specific PDE inhibitor, is no longer considered a primary therapy for COPD due to its wide range of side effects partially attributable to its lack of PDE4 specificity.[9] Roflumilast and its active N-oxide metabolite, are potent and competitive inhibitors of PDE4 and have little to no activity against PDEs 1, 2, 3, 5, and 7.[5,10] They selectively increase cAMP levels in lung tissue thereby, reducing the number of proinflammatory neutrophils and eosinophils. It is thought that agents that specifically target PDE4 such as roflumilast may be safer and more effective in the treatment of COPD than broad-spectrum PDE inhibitors like theophylline.[7]

Pharmacokinetics: Roflumilast has an absolute bioavailability of almost 80% following a 500 mcg oral dose.[5,11,12] The medication undergoes extensive hepatic metabolism via Phase I [cytochrome P450 (CYP)] and Phase II (conjugation) reactions. It is biotransformed by CYP1A2 and 3A4 to an N-oxide metabolite, which accounts for approximately 90% of its pharmacologic activity.[13] The maximum plasma concentration (C_{max}) of roflumilast is reached approximately 1 hour after dosing (range: 0.5 to 2 hours), while the maximum concentration of the N-oxide metabolite is reached in about 8 hours (range: 4 to 13 hours). Although food has no effect on total drug absorption, it delays roflumilast's time to maximum concentration (T_{max}) by 1 hour and reduces C_{max} by 40%; however, the N-oxide metabolite's T_{max} and C_{max} remain unaffected. Roflumilast and its N-oxide metabolite are 99% and 97% protein bound, respectively. The volume of distribution of a single 500 mcg dose is about 2.9 L/kg. Following oral administration, the apparent terminal plasma disposition half-life is approximately 10 to 20 hours for roflumilast and 20 to 44 hours for its active metabolite.[12] Steady state concentrations of roflumilast and the N-oxide metabolite are reached in approximately 4 and 6 days, respectively. About 70% of the roflumilast dose is eliminated in the urine.[5,14]

Select Clinical Trials: Fabbri and colleagues conducted two concurrent, multicenter studies in outpatients with moderate-to-severe COPD to evaluate once daily use of oral roflumilast 500 mcg versus placebo in patients treated with either inhaled salmeterol or tiotropium.[15] Main inclusion criteria included: >40 years old, COPD for at least 12 months prior to baseline visit, current or former smoking status (≥1 year smoking cessation) with ≥10 pack-year smoking history, postbronchodilator FEV_1 40-70% predicted value, postbronchodilator FEV_1/FVC ≤70%, partial reversibility to albuterol, and stable disease. Important exclusion criteria included: COPD exacerbation requiring treatment with systemic glucocorticoids and/or antibiotics 4 weeks prior to baseline visit, persistent lower respiratory tract infection 4 weeks prior to baseline visit, diagnosis of asthma and/or other relevant lung disease, current participation in a pulmonary rehabilitation program, known alpha-1-antitrypsin deficiency, human immunodeficiency virus (HIV) or active hepatitis infection, diagnosis or history of cancer within 5 years prior to study, pregnancy, breastfeeding, alcohol or drug abuse, and inability to follow study procedures. Patients recruited to the tiotropium plus roflumilast study were more symptomatic than those in the salmeterol plus roflumilast study being required to have chronic cough and sputum production with the use of at least 28 puffs per week of as-needed, short-acting beta-agonists during the run-in period while being treated with tiotropium for at least 3 months prior to study initiation. After a 4 week run-in period in which patients received placebo tablets, those with ≥80% compliance and stable COPD were randomized to roflumilast 500 mcg once daily in the morning or placebo along with either salmeterol or tiotropium for the next 24 weeks. Besides study medications and short-acting inhaled beta-agonists for acute exacerbations, other respiratory drugs (e.g., inhaled corticosteroids, short-acting anticholinergic drugs, other long-acting brochodilators) were not permitted. Patients were assessed on a monthly basis for 12 weeks and then every 6 weeks until week 24 using spirometric measurements recorded before and 30 minutes after inhalation of albuterol 400 mcg. New exacerbations, adverse events, body weight, adherence, completeness of daily diary, use of short-acting beta-agonists, Transition Dyspnea Index (TDI), and Shortness of Breath Questionnaire (SOBQ) data were recorded at every visit. The primary endpoint for both studies was change in mean prebronchodilator FEV_1 from baseline to each visit after randomization. Secondary endpoints included postbronchodilator FEV_1 and FVC, TDI score, SOBQ, rate of COPD exacerbations, and the use of rescue agents. Safety was assessed at each visit. Select efficacy results are listed in Table 1. There were no statistically significant differences in TDI focal score, change in SOBQ, or change from baseline in rescue medication use in the salmeterol plus roflumilast versus the placebo group. However, these endpoints were all significantly improved in the tiotropium plus roflumilast versus placebo group. A total of 63% of patients in the salmeterol plus roflumilast group reported adverse events compared to 59% of patients assigned to the salmeterol plus placebo group. In the tiotropium plus roflumilast group, 46% of patients reported adverse events compared to 41% of patients in the tiotropium plus placebo group. The most commonly reported adverse events were diarrhea, nausea, and weight loss in both studies. The authors concluded the addition of roflumilast to salmeterol or tiotropium improves lung function in patients with moderate-to-severe COPD.

A summary of other key clinical trials involving roflumilast is included in Table 2.

Table 1: Select Results from Fabbri Study[15]

Outcomes	SAL + ROF (n=466) versus SAL + Placebo (n=467)	TIO + ROF (n=371) versus TIO + Placebo (n=372)
Between-group difference in prebronchodilator FEV_1	49 mL p<0.0001 (95% CI 27-71)	80 mL p<0.0001 (95% CI 51-110)
Between-group difference in postbronchodilator FEV_1	60 mL p<0.0001 (95% CI 38-82)	81 mL p<0.0001 (95% CI 51-110)
Between-group difference in prebronchodilator FVC	47 mL p=0.0128 (95% CI 10-84)	95 mL p=0.0001 (95% CI 47-143)
Between-group difference in postbronchodilator FVC	58 mL p=0.0028 (95% CI 20-95)	101 mL p=0.0004 (95% CI 45-156)
Median time to 1st moderate or severe exacerbation (IQR)	83 days versus 71 days HR=0.60 p=0.0067 (95% CI 0.4-0.9)	NS
Median time to 1st mild, moderate, or severe exacerbation (IQR)	NS	50 days versus 37 days HR=0.7 p=0.0264 (95% CI 0.5-1.0)
Proportion of patients with moderate, or severe exacerbation	11% versus 18% RR=0.60 p=0.0015 (95% CI 0.43-0.82)	NS
Proportion of patients with mild, moderate, or severe exacerbation	28% versus 34% RR=0.82 p=0.0419 (95% CI 0.68-0.99)	22% versus 30% RR=0.75 p=0.0169 (95% CI 0.59-0.95)

SAL= Salmeterol ROF=Roflumilast TIO=Tiotropium FEV_1=Forced Expiratory Volume in One Second CI=Confidence Interval FVC=Forced Vital Capacity IQR=Interquartile Range HR=Hazard Ratio NS=Not Significant RR=Relative Risk

Table 2: Select Clinical Trials for Roflumilast in COPD[16-18]

Author, Year	Study Design	Objective	Conclusion
Rabe, 2005	Phase III, MC, DB, PC, RCT	To compare effects of roflumilast 250 mcg to roflumilast 500 mcg on postbronchodilator FEV_1 and health-related quality of life	Roflumilast improved lung function and reduced number of exacerbations compared to placebo
Calverley, 2009	MC, DB, PC, RCT*	To investigate whether roflumilast 500 mcg reduced the frequency of exacerbations requiring corticosteroids in patients with COPD	Roflumilast reduced exacerbation frequency and induced consistent and significant improvements in pre- and postbronchodilator FEV_1 in patients with symptoms of bronchitis and severe airflow limitation
Calverley, Sanchez-Toril, 2007	MC, DB, PC, PG, RCT	To determine if roflumilast 500 mcg improved lung function and decreased frequency of exacerbations over 1 year in patients with stable COPD	Roflumilast produced a modest but significant improvement in postbronchodilator lung function in patients with Stages III and IV COPD

*Two studies performed with identical design, different patient populations
COPD=Chronic Obstructive Pulmonary Disease MC=Multicenter DB=Double-Blind PC=Placebo-Controlled RCT=Randomized-Controlled Trial PG=Parallel Group FEV_1=Forced Expiratory Volume in One Second

Adverse Reactions: Weight loss was a common side effect occurring in 7.5% of patients treated with roflumilast in placebo-controlled clinical trials.[5] A one-year prospective assessment of those trials found that 20% of patients receiving roflumilast experienced a moderate weight loss of between 5 to 10% of body weight compared to 7% of those receiving placebo. Furthermore, 7% of roflumilast-treated patients compared to 2% of those receiving placebo, experienced a severe weight loss of >10% of body weight. Most patients regained some of their weight after roflumilast was discontinued. Other frequently reported adverse reactions to roflumilast in clinical trials include diarrhea (9.5%), dizziness (2.1%), insomnia (2.4%), decreased appetite (2.1%), nausea (4.7%), headache (4.4%), back pain (3.2%) and influenza (2.8%). Other reported adverse reactions include psychiatric disorders including anxiety, depression, and nervousness. Additionally, rare occurrences of suicidal ideation and behavior including completed suicide have been reported in clinical trials.[11]

Drug Interactions: Coadministration of roflumilast with rifampin resulted in a reduced PDE4 inhibitory activity of approximately 60%; therefore, coadministration with strong CYP450 inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) should be avoided.[5] Concurrent use of roflumilast with CYP3A4 inhibitors or dual inhibitors of CYP3A4 and CYP1A2 (e.g., erythromycin, ketoconazole, fluvoxamine, cimetidine) may significantly increase systemic exposure of roflumilast potentially increasing the risk of roflumilast-induced side effects. Concurrent use of oral contraceptives containing gestodene and ethinyl estradiol could increase side effects. Prior to the initiation of roflumilast with medications which may increase its systemic exposure, the risks of concurrent use should be weighed carefully against therapeutic benefit.

Pregnancy and Lactation: Roflumilast is classified as a pregnancy-risk category C, since there are no sufficient or well-controlled studies in pregnant women.[5] Although at therapeutic doses roflumilast has not been found to be teratogenic in mice, rats, or rabbits, reproductive toxicity at supratherapeutic doses has been reported in animals. Therefore, roflumilast should be avoided during pregnancy unless potential benefits outweigh the potential risk to the fetus. Roflumilast should not be used during lactation as the drug and its active metabolite are excreted into the breast milk of lactating rats and would most likely be transferred into human breast milk.

Monitoring Parameters: Patients taking roflumilast should be monitored for weight loss.[5] Discontinuation of roflumilast should be considered if unexplained or clinically significant weight loss occurs. Patients should also be observed for signs of depression, thoughts of suicide, and mood swings. Liver function tests should be routinely monitored.

Dose and Administration: The recommended dose of roflumilast is 500 mcg orally once daily without regard to meals.[5] The tablet should be taken at the same time each day, noting that it may take several weeks to achieve its therapeutic effect. No dose adjustment is recommended for patients with renal dysfunction. For patients with mild hepatic impairment (Child-Pugh Class A), no specific dosage adjustment is recommended; however, it should be used with caution. Roflumilast is contraindicated in patients with moderate-to-severe liver impairment (Child-Pugh B or C).

Place in Therapy: The 2011 GOLD guidelines indicate roflumilast may be useful in treating patients with Stages III or IV COPD to reduce COPD exacerbations in patients treated with oral corticosteroids and long-acting brochodilators.[3] Currently, it is not known whether roflumilast will provide an additional benefit to inhaled corticosteroid therapy. Roflumilast is not indicated for the treatment of acute bronchospasm or as monotherapy and should only be used as an adjuvant to bronchodilator therapy.[5,19]

Cost and Formulary Status: Roflumilast is available as a 500 mcg tablet. The average wholesale (AWP) price is about $6.90 per tablet or approximately $207 for a 30-day supply.[20] Roflumilast has recently been added to the CCHS Formulary restricted to continuation of therapy from home.

Conclusion: Roflumilast is an oral PDE4 inhibitor which is FDA-approved as a therapy to reduce the incidence of COPD exacerbations in patients with chronic bronchitis and a history of COPD exacerbations. This agent specifically inhibits PDE4 in airway inflammatory cells, thereby making it beneficial in disease states like COPD. Its specificity for PDE4 makes it a preferable option over theophylline, a broad spectrum PDE4 inhibitor with a narrow therapeutic index. In comparison to twice-daily inhaled glucocorticoids, roflumilast has the advantage of once-daily oral administration which may lead to increased patient compliance. The 2011 GOLD Guidelines indicate roflumilast may be useful in reducing exacerbations in patients with Stage III or IV COPD. However, it is associated with significant weight loss and gastrointestinal side effects. Therefore, potential benefits should be weighed against the potential risks prior to initiation of this novel therapy.

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Drug Information Center

Frequently Asked Question (FAQ)

What medications containing caffeine can be used to treat postdural puncture headaches (PDPH)?

A postdural puncture headache (PDPH) is a complication of spinal anesthesia or unintentional dural puncture during an attempted epidural anesthesia. A PDPH is usually treated with **intravenous caffeine and sodium benzoate 500 mg** in 1000 mL normal saline administered over 1 hour, followed by 1000 mL normal saline infused over 1 hour; a second course of caffeine can be given for unrelieved headache pain in 4 hours. The 500 mg caffeine and sodium benzoate dose contains **250 mg anhydrous caffeine**. The sodium benzoate 250 mg helps increase the solubility of the caffeine. When caffeine and sodium benzoate is not available, **300 mg of oral anhydrous caffeine** as a single dose can be used. Caffeine citrate solution is available as 20 mg/mL and contains 10 mg/mL of caffeine base. Therefore, **30 mL of caffeine citrate** 20 mg/mL oral solution contains 300 mg of anhydrous caffeine.

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Formulary Update

The CCHS Medical Staff Pharmacy and Therapeutics Committee met on March 20, 2012, and the Cleveland Clinic Local Pharmacy and Therapeutics Committee met on April 3, 2012 and the following decisions were made:

<u>Additions to the CCHS Adult Formulary</u>:

Neurosciences:

1. **Iloperidone (Fanapt®; Novartis):** It is an atypical antipsychotic agent FDA-approved for the treatment of schizophrenia in adults. The recommended target dosage of iloperidone is 12 to 24 mg/day administered twice daily which is achieved after slow daily dosage increases in order to avoid orthostatic hypotension. It is also recommended that the initiation titration schedule be followed whenever patients have had interruption of iloperidone therapy of more than 3 days. Dosage adjustment is necessary when iloperidone is administered in patients receiving a concomitant strong CYP2D6 or CYP3A4 inhibitor. An order panel will be created within EPIC to facilitate ordering of the titration schedule for initiation of therapy.
    a. Iloperidone is **restricted** to Psychiatry for initiation of therapy; however, continuation of therapy from home is not restricted.

Critical Care/Surgery/Anesthesia:

1. **Promethazine injection:** In 2007, promethazine injection (Phenergan®) was removed from the Formulary due to potential safety issues if the medication was given undiluted (e.g., extravasation) and at the time this decision was made in part because the Department of Pharmacy could not ensure timely dispensing of diluted promethazine to all patient care areas. However, promethazine injection can be an effective agent in the management of nausea and vomiting when properly diluted and administered slowly through a large bore vein and therefore, the CCHS Medical Staff Pharmacy and Therapeutics Committee decided to add it back to the Formulary.

Cardiovascular/Vascular Medicine:

1. **Rivaroxaban (Xarelto®; Janssen):**
    a. Rivaroxaban is already on the CCHS Formulary restricted for use as thromboprophylaxis after orthopedic surgery. It has now been added to the Formulary for nonvalvular atrial fibrillation to reduce the risk of stroke and systemic embolism. Of note, there is different dosing and renal dose adjustments for the two FDA-approved indications. Epic drug records will be configured appropriately to inform prescribers and pharmacists about the difference in dosing for the two indications, the recommended renal dose adjustments, and the requirements for administration with food. Pharmacists will need to review and document the patient's renal function and document the current creatinine clearance in an I-vent associated with the rivaroxaban order. A Best Practice Alert (BPA) will be added to remind pharmacists of this requirement during order verification.
        i.) **Deep vein thrombosis (DVT) prophylaxis:** Usual dose is 10 mg by mouth daily with or without food. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established. Patients with moderate renal impairment (CrCl 30 to 50 mL/min) should undergo close observation and evaluation for any signs/symptoms of blood loss. The use of rivaroxaban for DVT prophylaxis in patients with severe renal impairment (CrCl <30 mL/min) should be avoided.
        ii.) **Nonvalvular atrial fibrillation:** Usual dose for patients with CrCl >50 mL/min is 20 mg by mouth daily with the evening meal. For patients with CrCl 15 to 50 mL/min, the recommended dose is 15 mg once daily with the evening meal. The use of rivaroxaban for nonvalvular atrial fibrillation in patients with CrCl <15 mL/min should be avoided.

Changes in Current CCHS Adult Formulary Restrictions:

1. **Bevacizumab (Avastin®; Genentech):** Current CCHS Formulary restrictions have been expanded to include use by the Department of Otolaryngology for patients with recurrent respiratory papillomatosis (RRP) of the vocal folds.
2. **Dofetilide (Tikosyn®; Pfizer):** To meet needs of CCHS patients, one dose of dofetilide may be ordered by a non-Tikosyn® certified prescriber during off-hours. However, follow-up will need to occur the next day and any subsequent dofetilide therapy will have to be ordered by a Tikosyn® certified prescriber. This has been the practice at the Main Campus and will be expanded to the other CCHS hospitals.

Cleveland Clinic Children's Hospital (Pediatrics):

<u>Additions to CCHS Pediatric Formulary</u>:

1. **Asparaginase *Erwinia chrysanthemi* (Erwinaze™; EUSA):** It is FDA-approved as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to E. coli-derived asparaginase. Erwinaze™ contains an asparaginase specific enzyme derived from Erwinia chrysanthemi which catalyzes the deamidation of asparagine to aspartic acid and ammonia, resulting in a reduction in circulating levels of asparagine. Cytotoxicity of leukemic cells results because they are unable to synthesize asparagine and require an exogenous source for protein metabolism. To substitute for *one* dose of pegaspargase: administer Erwinaze™ 25,000 units/m^2 intramuscular (IM) three times a week on Monday/ Wednesday/Friday for 6 doses. To substitute for a dose of native *E. coli* asparaginase: administer Erwinaze™ 25,000 units/m^2 IM for each dose.
    a. Asparaginase *Erwinia chrysanthemi* will be **restricted** to Department of Pediatric Hematology/Oncology for **outpatient use only** in patients with acute lymphoblastic leukemia (ALL) who have developed hypersensitivity to *E. Coli*-derived asparaginase.

2. **Clobazam (Onfi™; Lundbeck Inc.):** It is a 1,5-benzodiazepine FDA-approved for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older and is classified as a Schedule IV controlled substance under the Controlled Substance Act. Dosing of clobazam is based on body weight. Patients whose body weight is 30 kg or less should be started at 5 mg daily and titrated to 20 mg daily. Patients whose body weight is greater than 30 kg should be started on 10 mg daily and titrated up to 40 mg daily. Titration should occur at weekly increases, with the prescribed dose doubled, if therapy is tolerated. Total daily doses greater than 5 mg should be given in 2 divided doses each day. Clobazam can be administered whole or crushed and mixed with applesauce.
    a. Clobazam is **restricted** to continuation of home therapy. It will remain non-formulary for initiation of therapy in the inpatient setting.

Not Added to the CCHS Pediatric Formulary:

1. **Bortezomib (Velcade®; Millenium Pharmaceuticals)** was requested for treatment of highly sensitized pediatric patients pre- and post-heart transplant. Due to limited pediatric efficacy and safety data the committee recommended a formal study assessing bortezomib use in these patients be submitted to the IRB. Bortezomib should not be dispensed for pediatric patients. Any requests to use bortezomib in pediatric patients should be forwarded to the Drug Information Center.
2. **IncobotulinumtoxinA (Xeomin®; Merz Pharmaceuticals):** There are no pediatric efficacy or safety data available at this time. Xeomin® should not be dispensed for pediatric patients. Onabotulinumtoxin A (Botox®) remains on the pediatric formulary restricted to the Departments of Pediatric Neurology, Physiatry, and Ears, Nose, and Throat (ENT) for outpatient treatment of spasticity, dystonias, and drooling.

Changes in Current CCHS Pediatric Formulary Restrictions:

1. **Intravenous acetaminophen (Ofirmev™; Cadence Pharmaceuticals):**
   Current restriction: Patient with severe constipation or other adverse side effects related to opioids for whom ketorolac use is either contraindicated or not fully effectual in controlling pain.
   Re-worded restriction: Patient with severe constipation or other adverse side effects related to opioids for whom ketorolac use is either contraindicated or not fully effectual in controlling pain **and patient is NPO.**

Deletions from the CCHS Pediatric Formulary:

1. **Silver nitrate**: Due to safety concerns silver nitrate will no longer be used as a hemostatic agent post-circumcision in pediatric patients. There are other hemostatic therapeutic options for post-circumcision care. Gauze and pressure are usually effective. Other options that are not dispensed from pharmacy include Surgicel® or Gelfoam®. Topical thrombin may also be used; however, it is the most expensive option. Silver nitrate remains on the formulary for other indications.
2. **Injectable promethazine (Phenergan®):** There are patient safety concerns as well as a Black Box Warning that injectable promethazine should not be used in pediatric patients <2 years of age. Injectable promethazine should not be administered to any pediatric patients.
3. **Drotrecogin alfa (Xigris®):** This medication has been removed from the US market.

Therapeutic Interchange Programs for CCHS Pediatric Formulary

1. **Inhaled Corticosteroids:** There **will not** be any therapeutic interchange programs in pediatrics for inhaled corticosteroids.

2. **5-HT3 Receptor Antagonists:** Palonosetron (Aloxi®; Eisai) has been added to the pediatric automatic therapeutic interchange program for chemotherapy-induced nausea and vomiting (CINV). Any inpatient orders for palonosetron for CINV will automatically be converted to ondansetron.