

CPS Insider is a quarterly client newsletter produced by the University of Massachusetts Medical School (UMMS) Clinical Pharmacy Services (CPS).

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At a Glance



Noteworthy

The POISE Trial: Health risks of perioperative metoprolol ER use



What's New at UMMS?

CPS' plan for prescriber education and MTM programs

New Generics

- **Estradiol and norethindrone acetate (Activella®)**
 Approved 4/17/2008
 Launched 4/17/2008
- **Ropinirole hydrochloride (Requip®)**
 Approved 5/5/2008
 Launched 5/5/2008
- **Acarbose (Precose®)**
 Approved 5/7/2008
 Launched 5/7/2008
- **Drospirone and ethinyl estradiol (Yasmin®)**
 Approved 5/9/2008
 Launched after 7/1/2008
- **Paroxetine (Paxil CR®)**
 Approved 6/29/2007
 Launched 5/14/2008*

* Mylan has 180-day marketing exclusivity for 12.5 mg and 25 mg

Drug Watch



Relistor® (methylnaltrexone Br)

Approved: 4/24/2008
 Manufacturer: Wyeth, Inc.
 Formulation: SC Injection
 Cost (AWP): \$50/injection

Methylnaltrexone bromide is a novel, peripherally acting, selective μ -opioid receptor antagonist that reduces the constipating effects of opioids without impacting opioid-mediated analgesic effects.

Methylnaltrexone is FDA-approved for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care, when response to laxative therapy has not been sufficient.

The recommended dose for patients weighing ≥ 38 to < 62 kg is 8 mg SC every other day as needed, and 12 mg for patients weighing ≥ 62 to 114 kg. Patients weighing < 38 kg or ≥ 62 kg should be dosed at 0.15 mg/kg. Doses should not be given more frequently than one dose in a 24-hour period. It is available as a single-use vial and an injection kit containing 7 single-use vials.

The most common side effects of methylnaltrexone include abdominal pain, flatulence, nausea, dizziness and diarrhea.

Methylnaltrexone is a weak inhibitor of CYP2D6 and is eliminated primarily as unchanged drug in the urine and feces. However, no dosage adjustments are necessary in patients with mild to moderate renal or hepatic impairment.



Cimzia® (certolizumab pegol)

Approved: 4/22/2008
 Manufacturer: UCB, Inc.
 Formulation: SC Injection
 Cost (AWP): \$1,579/400 mg dose

Certolizumab pegol is a tumor necrosis factor- α (TNF- α) inhibitor that interferes in the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor and nitric oxide.

Certolizumab is FDA-approved for reducing signs and symptoms of moderate to severe Crohn's disease and maintaining clinical response in adult patients who have failed conventional therapy.

The recommended initial dose is 400 mg (given as two injections of 200 mg) SC once and then repeated at weeks two and four. The recommended maintenance dose is 400 mg SC every four weeks. It is available as a lyophilized powder for solution.

Current TNF inhibitors for the treatment of Crohn's disease require daily or weekly administration. The advantage of certolizumab is the dosing frequency due to the addition of polyethylene glycol, which delays its excretion from the body.

The most common side effects of certolizumab include arthralgia, upper respiratory tract infection and urinary tract infection. Certolizumab has a blackbox warning for the potential risk of serious infections including tuberculosis (TB), invasive fungal and other opportunistic infections.

New FDA-Approved Indications

- **Orencia® (abatacept)**
Approved on 4/8/2008. Reduction of signs and symptoms in pediatric patients six years and older with moderately to severely active polyarticular juvenile idiopathic arthritis; may be used as monotherapy or concomitantly with methotrexate.
- **Vyvanse® (lisdexamfetamine dimesylate)**
Approved on 4/23/2008. Treatment of attention deficit hyperactivity disorder in adults.
- **Amitiza® (lubiprostone)**
Approved on 4/29/2008. Treatment of irritable bowel syndrome with constipation in adult women 18 years and older.

New Formulations and Dosages

- **Patanase® (olopatadine)**
0.6 % nasal spray
Approved 4/15/2008
- **Treximet® (sumatriptan succinate/naproxen sodium)**
85/500 mg tablets
Approved 4/15/2008
- **Aplenzin® (bupropion hydrobromide)**
174 mg, 348 mg, 522 mg tablets
Approved 4/23/2008

Information available at: www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm



Clinical Notes

THE GLOBAL STRATEGY FOR DIAGNOSIS, MANAGEMENT AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) - 12/2007

Summary of 2007 Guideline Updates: Selected Key Points

- Depression has been more recently identified as a comorbid condition in COPD. Depression may complicate COPD management. Currently, the guideline does not provide information on an integrated approach to managing the comorbid conditions. Close monitoring is recommended.
- Inhaled bronchodilators are the bronchodilators of choice in COPD. Theophylline is not recommended as a bronchodilator in COPD. Theophylline is ineffective as a bronchodilator at low doses and is associated with potential toxicities at high doses.
- Due to limited supporting data, nedocromil, leukotriene modifiers and anti-TNF- α antibody (infliximab) are not recommended for use in patients with COPD.
- Associated with a significant reduction of complications (e.g., hyperglycemia), nebulized budesonide may be used as an alternative to, though is more costly than, oral glucocorticosteroids in the treatment of non-acidotic exacerbations of COPD.
- Levalbuterol has been added to the list of short-acting β_2 -agonists.
- Medical and economic outcomes of self-management programs for COPD are being tracked to determine impact on disease control.

Chapter-by-Chapter Selected Key Points

- **DEFINITION/ASSESS AND MONITOR DISEASE:** COPD is a preventable and treatable disease. The clinical diagnosis of COPD should be confirmed by spirometry. Irreversible airflow limitation in COPD is defined by postbronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted.
- **BURDEN OF COPD/RISK FACTORS/ PATHOLOGY, PATHOGENESIS AND PATHOPHYSIOLOGY/ REDUCE RISK FACTORS:** Cigarette smoking is the most common risk factor for COPD worldwide. Severe hereditary deficiency of α_1 -antitrypsin is the most well documented COPD genetic risk factor. Smoking cessation is the most effective and cost effective intervention strategy for most people. Limiting passive smoking is also important.
- **MANAGE STABLE COPD:** Pharmacotherapy for COPD is used to reduce symptoms/ complications; existing therapies have not been reported to modify the clinical course of lung function over time. Scheduled or PRN bronchodilators (i.e., β_2 -agonists, anticholinergics, methylxanthines) are used for symptomatic management. The addition of an inhaled glucocorticosteroid may be used for certain symptomatic patients with repeated exacerbations. Appropriate influenza and pneumococcal vaccinations are recommended.
- **MANAGE EXACERBATIONS:** Inhaled β_2 -agonists (with or without anticholinergics) and oral glucocorticosteroids are effective treatment options for COPD exacerbations. Antibiotics may be used in patients with clinical signs of airway infection.

For additional information, please visit: www.goldcopd.org

Advisories

Exubera® (insulin human rDNA origin)

On 4/9/2008, Pfizer informed health care professionals and patients of updated safety information in the warnings section for Exubera® U.S. Prescribing Information. In clinical trials of Exubera®, there were reports of six newly diagnosed cases of primary lung malignancies in patients treated with Exubera® while there was only one newly diagnosed case among patients treated with comparator agents. There was also one post-marketing report of a primary lung malignancy in an Exubera®-treated patient. All newly diagnosed lung cancer patients had a prior history of cigarette smoking.

Relenza® (zanamivir)

On 4/1/2008, the FDA informed health care professionals of important revisions to the warnings and

precautions sections in the prescribing information for zanamivir. The revisions resulted from post-marketing reports of delirium and abnormal behavior leading to injury in patients with influenza who were taking neuraminidase inhibitors, including zanamivir. The events were mostly observed in pediatric patients and were often associated with a quick onset and resolution. A direct connection between the events and zanamivir has not been established. Patients should be closely monitored for neuropsychiatric symptoms.

Neupro® (rotigotine transdermal system)

On 4/9/2008, the FDA issued an alert highlighting the planned recall of rotigotine at the end of April 2008. Patients taking rotigotine should be gradually down-titrated. Abrupt discontinuation is not recommended due to the risk of neuroleptic malignant syndrome. The recall is a result of the

formation of rotigotine crystals in the patches. When the drug crystallizes, the amount of drug available to be absorbed through the skin decreases resulting in variances in efficacy.

Enbrel® (etanercept)

On 3/14/2008, Amgen Inc. and Wyeth Pharmaceuticals issued a warning to alert health care professionals to recent revisions to the U.S. Prescribing Information (U.S. PI) for etanercept and future plans to develop an accompanying Medication Guide for patients. The revisions include: a Boxed Warning highlighting the risk of infections, including bacterial sepsis and tuberculosis, with etanercept use; a revision to the Adverse Reactions section clarifying that tuberculosis was observed in 0.007% to 0.01% of patients taking etanercept based upon global clinical studies conducted in U.S. and Canada. This warning should promote education and close monitoring for infections.



From The Hill

Federal

The Sentinel System: A National Electronic System to Monitor Product Safety

The Sentinel Initiative involves a new electronic surveillance system called the Sentinel System. Through this system, the FDA may actively gather information relating to the use of drugs and medical products following their approval. For example, the FDA may query specific adverse event data from large electronic claims databases and medical records maintained by participating private and federal entities. Hospital, physician and medication data from varying branches of Medicare (Parts A, B and D, respectively) will be linked into a much larger data set and will provide important information on product safety. Importantly, all de-identified data will be managed in accordance with privacy and security safeguards that currently exist. This may allow the FDA to conduct a targeted query with participating Sentinel partners. It is expected that this new system will augment existing surveillance methods and allow for a more robust monitoring system.

For the complete FDA white paper, visit: www.fda.gov/oc/initiatives/advance/reports/report0508.html

State

Massachusetts: The Massachusetts Medical Society has filed a suit over its displeasure with the Group Insurance Commission's (GIC) physician ranking system. The GIC and its associated health plans manage the health insurance for thousands of public employees. These organizations utilize a physician ranking system for the measures of cost and quality. A tiered health plan may rank individual physicians rather than physicians' practices. The lawsuit claims that this ranking system may have caused some physicians to be defamed and some patients to be defrauded. For example, some patients may have been forced to pay a higher co-payment based on their physician's rank, and some prescribers may have been negatively affected through their willingness to treat patients with costly and complex diseases.

For more information, please visit: www.massmed.org/AM/Template.cfm?Section=Pay_for_Performance&CONTENTID=21878&TEMPLATE=/CM/ContentDisplay.cfm

Pipeline

Flutiform® (fluticasone propionate and formoterol fumarate inhalation aerosol)

Flutiform® is a fixed-dose inhaled corticosteroid and long-acting β_2 -adrenergic agonist in a metered dose inhaler. It would offer the efficacy and safety of the fluticasone component and the fast-acting onset of action of the formoterol reliever component. The specially designed inhaler will incorporate a dose indicator to improve patient compliance. Flutiform® is expected to bring additional competition to the Advair® (fluticasone and salmeterol) and Symbicort® (budesonide and formoterol) market as early as first quarter of 2009.

Indacaterol

Indacaterol is an inhaled, long-acting β_2 -adrenergic agonist in initial stages of development. It would be the first agent of its kind to provide 24-hour efficacy with a single daily dose. In studies, the tolerability and safety profiles have been favorable. Indacaterol is being studied as monotherapy and in combination with other agents used in the treatment of asthma and COPD.

Acclidinium

Acclidinium is a novel, inhaled anticholinergic bronchodilator that is in phase III clinical development for once daily maintenance treatment of COPD. Trial results should be available by the end of the year.

Noteworthy

Effects of extended-release (ER) metoprolol succinate in patients undergoing non-cardiac surgery (POISE TRIAL): a randomized controlled trial¹

Perioperative β -blockers have been used in non-cardiac surgery to suppress the effects of increased catecholamines and subsequently prevent cardiovascular events. However, trials of β -blockers in patients undergoing non-cardiac surgery have reported conflicting results. The POISE trial is a randomized placebo-controlled trial comparing the effect of metoprolol succinate ER to placebo on 30-day risk of major cardiovascular events. The trial included 8,351 patients with, or at risk of, atherosclerotic disease who underwent non-cardiac surgery. Results showed that fewer patients in the metoprolol ER group experienced the primary endpoints of cardiovascular death, non-fatal myocardial infarction or non-fatal cardiac arrest compared to placebo ($P=0.0399$). However, perioperative metoprolol ER resulted in a significantly increased risk of total death, stroke and clinically significant hypotension and bradycardia compared to placebo ($P=0.0317$, $P=0.0053$, $P<0.0001$ and $P<0.0001$, respectively). The authors concluded that the addition of perioperative metoprolol ER has potential benefits and risks. Current perioperative guidelines that recommend β -blocker therapy in patients undergoing non-cardiac surgery may need to be revised in light of these findings.

1. POISE Study Group, Devereaux PJ, et al. Lancet. 2008 May 31;371(9627):1839-47. Epub 2008 May 12.

What's New at UMMS?

CPS' work with New York (NY) Medicaid has continued at a rapid pace over the past month. Work plans and budgets for the prescriber education and the medication therapy management (MTM) programs have been submitted and are awaiting final approval from the NY Department of Health (DOH) and the State University of New York (SUNY). We are still on track for a July/August start date for both of these programs and will be recruiting for positions soon to help us roll out these initiatives. We have been meeting jointly with NY, SUNY and Harvard University to discuss the development of the prescriber education/academic detailing program. Harvard has extensive experience in this area, having created and managed multiple programs across the country. At some point, we may seek to build a multi-state collaborative around academic detailing potentially including MA, PA, NY and the other New England states.



UMMS Clinical Pharmacy Services: Who We Are and What We Do

The University of Massachusetts Medical School (UMMS) Clinical Pharmacy Services (CPS) is a comprehensive prescription drug management program developed in 1999 as part of UMMS' Commonwealth Medicine division, primarily to provide drug utilization review for Massachusetts Medicaid. Today, CPS brings exceptional depth and experience in the development and implementation of unique, client-customized managed care-related clinical pharmacy functions including, but not limited to, evidence-based formulary support, drug utilization review, medication therapy management, clinical call center support and provider/patient education. 'CPS Insider' is an educational resource produced quarterly in an effort to deliver critical information at the highest level of quality to our clients. We hope that you find this resource of value and welcome your suggestions for improvement.

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