

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 SEAS Trial: Cancer risk associated with the use of Vytorin®



What's New at UMMS?

Academic Detailing to start November 1 in New York

New Generics

- **Lamotrigine (Lamictal®)**
 Approved: 8/30/2006
 Launched: 7/22/2008*
- **Dronabinol (Marinol®)**
 Approved: 6/27/2008
 Launched: 8/1/2008
- **Risperidone (Risperdal®)**
 Approved: 6/30/2008
 Launched: 6/30/2008
- **Nisoldipine (Sular®)**
 Approved: 7/25/2008
 Launched: 7/25/2008
- **Mycophenolate Mofetil (CellCept®)**
 Approved: 7/29/2008
 Launch: TBD
- **Divalproex Sodium (Depakote®)**
 Approved: 7/29/2008
 Launched: 7/29/2008

* Teva has 180-day pediatric exclusivity until 1/22/2009

Drug Watch



Nplate™ (romiplostim)

Approved: 8/22/2008

Manufacturer: Amgen, Inc.

Formulation: SC Injection

Cost (AWP): \$1275/250 µg

Romiplostim is a novel thrombopoietin (TPO) receptor agonist that mimics the actions of TPO to stimulate platelet production. Romiplostim is FDA-approved for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP).

The recommended dose is a weekly SC injection of 1 µg/kg and may be increased by 1 µg/kg/wk to achieve the target platelet count. The maximum recommended dose is 10 µg/kg/wk. It is available in single use vials of 250 µg and 500 µg.

Romiplostim is only available through the Nplate™ NEXUS (Network of Experts Understanding and Supporting Nplate and Patients) program-- a restricted distribution program that requires all prescribers and patients to register in order to prescribe and administer/receive romiplostim.

Common adverse events include arthralgia, myalgia, pain in extremities and dizziness. Platelet and CBC monitoring is required since romiplostim may be associated with marrow fibrosis. Drug interactions with romiplostim are unknown at this time.

Romiplostim provides a new approach to treatment of ITP and an additional option when corticosteroids, immunoglobulins or splenectomy have failed.



Xenazine® (tetrabenazine)

Approved: 8/15/2008

Manufacturer: OVATION, Inc.

Formulation: Oral Tablet

Cost (AWP): TBD (mid-Nov)

Tetrabenazine is a novel monoamine depletor that interferes with the vesicular monoamine transporter type two (VMAT 2) resulting in decreased monoamine uptake.

It is an orphan drug FDA-approved for the treatment of chorea associated with Huntington's disease. Chorea is an involuntary movement disorder that causes rapid, uncontrollable muscular contractions. The recommended starting dose is 12.5 mg daily and may be increased in weekly intervals of 12.5 mg with a maximum daily dose of 100 mg. Doses greater than 37.5 mg should be divided into three administrations.

The most common adverse events include sedation, akathisia, depression and fatigue. Tetrabenazine has a **Black Box** warning for the increased risk of depression and suicidal tendencies and patients should be monitored carefully for these effects.

Tetrabenazine is metabolized primarily by CYP2D6; patients who are to receive a daily dose greater than 50 mg should undergo genotyping for CYP2D6 to determine metabolizing capability.

Tetrabenazine provides an option to patients previously limited to supportive therapy or dopamine antagonists. It is estimated to be available by the end of this year.

New FDA-Approved Indications

- **Cymbalta® (duloxetine)**
Approved on 6/13/2008. Duloxetine is indicated for the treatment of fibromyalgia.
- **Avodart® (dutasteride)**
Approved on 6/19/2008. Dutasteride is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in combination with tamsulosin.
- **Viread® (tenofovir)**
Approved on 8/11/08. Tenofovir is indicated for the treatment of chronic hepatitis B.

New Formulations and Dosages

- **Aloxi® (palonosetron)**
0.5 mg capsule
Approved: 8/22/2008
- **Requip® XL™ (ropinirole extended release)**
2 mg, 3 mg, 4 mg, 8 mg tablets
Approved: 7/1/2008

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

Clinical Notes

ANTIRETROVIRAL TREATMENT OF ADULT HIV INFECTION – 8/2008

2008 Recommendations of the International AIDS Society-USA Panel

- Updates to the 2006 version of this guideline were made based upon new recommendations and developments in the following areas: (1) FDA approval of three novel antiretroviral agents, including maraviroc, raltegravir and etravirine; (2) revised treatment algorithms for antiretroviral-naïve and -experienced patients; (3) role of HIV in the progression of non-AIDS diseases.
- The focus of HIV treatment is shifting from drug toxicity and resistance development to the risk of untreated viremia and virus-associated progression of non-HIV disease and end organ damage. Treatment should be initiated for asymptomatic patients before the CD4 cell count falls <350 cells/ μ L and the decision of when to initiate treatment should be based on the patient's acceptance of treatment and the presence of additional risk factors. Initiation of therapy is recommended in asymptomatic patients with a high plasma viral load; rapidly declining CD4 cell count; active hepatitis B or C infection; risk of cardiovascular disease, HIV-associated nephropathy, and/or specific opportunistic infections; and pregnant patients with detectable levels of HIV-1 RNA. All symptomatic patients should be treated regardless of CD4 cell count.
- Initial treatment regimens for treatment-naïve patients, consisting of three fully active agents as determined by resistance testing, should contain two nucleoside reverse transcriptase inhibitors (NRTIs) in addition to efavirenz or a ritonavir-boosted protease inhibitor (RBPI).
- Nevirapine may be an alternative to efavirenz in women contemplating pregnancy or in the first trimester of pregnancy.
- Appropriate RBPIs can include lopinavir, atazanavir, fosamprenavir, darunavir or saquinavir. Lopinavir, available as a coformulation with ritonavir, may be associated with diarrhea and hypertriglyceridemia. In comparison, atazanavir, which should not be taken with acid reducing agents, and saquinavir, cause less diarrhea and fewer triglyceride elevations.
- Recommended nRTI combinations include tenofovir/emtricitabine and abacavir/lamivudine. In one study, abacavir/lamivudine was shown to be inferior to tenofovir/emtricitabine in patients with viral loads >100,000 copies/mL. HLA-B*5701 screening is recommended prior to abacavir treatment to reduce the risk of an immune-mediated hypersensitivity reaction.
- Maraviroc, a CC chemokine receptor-5 (CCR5) antagonist, is a new treatment option for patients with documented resistance to other antiretroviral therapies and whose viral strains use the CCR5 receptor to enter the CD4 cell. Patients should be screened for tropism prior to treatment. Two other novel agents used for treatment-experienced patients include: raltegravir, an integrase strand transfer inhibitor, and etravirine, a second generation nonnucleoside reverse transcriptase inhibitor.
- Genotypic testing for resistance should be performed in treatment-naïve patients and when a new regimen is introduced after treatment failure with HIV-1 RNA levels of >500 to 1000 copies/mL. The goal of treatment is to maintain an HIV-1 RNA level <50 copies/mL.

Antiretroviral treatment of adult HIV infection: 2008 recommendations of the International AIDS Society-USA panel. JAMA. 2008 Aug 6;300(5):555-570.

Advisories

Byetta® (exenatide)

On 8/8/2008, the FDA issued an update to a previous alert made in 2007 regarding the risk of pancreatitis in patients using Byetta® (exenatide) for the management of type 2 diabetes. The original 2007 alert resulted in an amendment to the prescribing information of exenatide to include pancreatitis as a precaution. In this newest alert, the FDA has referenced six new cases of hemorrhagic or necrotizing pancreatitis in patients who were on exenatide; two of which were associated with a fatal outcome. Amylin Pharmaceuticals, Inc. and Eli Lilly and Company, the manufacturers of Byetta®, were aware of the cases referenced by the FDA. To date, the FDA has been notified of a total of six cases of patients developing pancreatitis

while on exenatide that have resulted in death. They note that, in four of these patients, death did not appear to be directly attributable to the development of pancreatitis. In their newest safety update, Amylin and Lilly recommend patients who are taking exenatide be observed for and educated on signs and symptoms of pancreatitis. If pancreatitis is suspected, exenatide should be discontinued. The medication should not be resumed in patients with confirmed pancreatitis.

Fluoroquinolone Antimicrobial Drugs

On 7/8/2008 after a recent evaluation of the medical literature and post-marketing adverse event reports, the FDA notified the makers of fluoroquinolone antimicrobial drugs of the need for additional warnings regarding the safety of these agents.

Specifically, the addition of a Boxed Warning describing the increased risk of developing tendinitis and tendon rupture has been requested. The development of a Medication Guide to be distributed to patients has also been requested. These additional warnings strengthen the existing warning information included in the fluoroquinolone prescribing information. Due to continued reports of tendinitis and tendon rupture, the FDA stresses the need for health care providers to weigh the potential risks and benefits of using these agents in individual patients. The FDA also urges prescribers only to use these agents for the treatment and/or prevention of infections suspected to be caused by bacteria susceptible to these agents. The Boxed Warning is exclusive to the fluoroquinolones for systemic use; it does not apply to fluoroquinolones for ophthalmic or otic use.



From The Hill

Federal

Additional Medicare Reimbursement for E-Prescribing

On 1/01/2009, the federal government will begin reimbursing Medicare prescribers who utilize an electronic prescribing system when sending prescriptions to the pharmacy. Prescribers who use E-prescribing will receive an additional 2 percent in addition to standard reimbursement rates from 2009-2010, 1 percent in 2011-2012 and 0.5 percent in 2013. These incentives have been initiated in order to encourage the gradual transition to electronic prescribing, which prescribers have remarked is too costly to implement. Medicare is expecting to save as much as \$156 million over the next five years through avoided drug errors. Furthermore, this initiative will cut down on the estimated 1.5 million injuries each year due to drug related errors as well as decrease the 150 million phone calls pharmacies make each year to prescribers for prescription clarification. Prescribers who choose not to use the technology will see a reduction in their reimbursement starting with 1 percent in 2012, 1.5 percent in 2013 and 2 percent in 2014.

For additional information, please visit <http://www.aishealth.com/GNOW/080408.html>

New PhRMA Code of Ethics

The Pharmaceutical Research and Manufacturers of America (PhRMA) have revised their code of ethics, which was released on 7/10/2008, and will take effect 1/1/2009. Based on the new code, pharmaceutical companies will no longer be able to provide physicians with pens, pads and other items that have a company logo on them. Manufacturers will still be able to provide educational materials; however, their value must not exceed \$100. Companies will no longer be able to provide restaurant meal or sporting and entertainment event tickets to health care professionals. The new code will also place a limit on how much a company can compensate speakers and consultants. Finally, for companies that provide continuing education funding, the code states that a full range of treatment options should be included in the program and that it should not solely promote the product manufactured by the sponsoring company.

For additional information, please visit <http://www.faeagre.com/showarticle.aspx?Show=7787>

Pipeline

Vernakalant hydrochloride

Vernakalant HCl, an oral agent for the maintenance therapy of atrial fibrillation, is being developed by Cardiome Pharma Corporation. Vernakalant acts by blocking ion channels in the heart to restore normal rhythm. It is currently under development as an intravenous formulation for the acute conversion of atrial fibrillation as well. Available studies have not examined the use of this agent in patients with heart failure, a common comorbidity in patients with atrial fibrillation. The FDA has issued an approvable letter regarding the intravenous formulation requesting additional safety data. The oral formulation has progressed to the late stages of clinical development based on positive Phase II results.

Naproxcinod

Naproxcinod, an oral anti-inflammatory agent for the treatment of osteoarthritis symptoms, is currently being developed by NicOx. It is a cyclooxygenase inhibiting nitric oxide donator (CINOD) and is currently the only drug in this class.

Phase III studies have shown naproxcinod to be superior to placebo as well as non-inferior to naproxen, 500 mg twice daily, based on results of WOMACTM pain and function assessments. In addition, a 52-week open label extension study showed that naproxcinod does not increase patient blood pressure over time while continuing to sustain efficacy throughout this period. Full results of the completed Phase III studies are anticipated before the end of this year.

Noteworthy

Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis (SEAS): a randomized, placebo-controlled study

Aortic-stenosis, a common condition among the elderly, is associated with an increased risk of death due to cardiovascular events. By lowering patients' lipid levels, progression of aortic-valve stenosis may be delayed, thereby reducing the need for aortic-valve replacement. The 1,873-patient SEAS study aimed to show that daily treatment with simvastatin/ezetimibe (Vytorin®) offers a nonsurgical way to treat aortic stenosis by reducing bad cholesterol and plaque buildup. However, results of the study showed the medication did not reduce the composite outcome of combined aortic-valve events and ischemic events in patients with mild-to-moderate aortic-valve stenosis. An overall reduced cardiovascular risk was not found with simvastatin/ezetimibe. Results troubled researchers when they observed an increased incidence of cancer among patients in the simvastatin/ezetimibe group ($P=0.01$). After reviewing preliminary results, the FDA has informed health care professionals of the possible association between the use of simvastatin/ezetimibe and a potentially increased incidence of cancer. For now, health care professionals should continue to monitor patients taking Vytorin®. The FDA will communicate its final recommendations after evaluating the final study report.

1. Rossebo AB, et al. NEJM. 2008;359:1343-1356.

What's New at UMMS?

There has been much activity over the past few months surrounding CPS' work with the New York State Department of Health and the creation of an Academic Detailing program for the state of New York. Scheduled to start November 1, the first topic is the treatment and prevention of RSV bronchiolitis. The program's creation has been a collaborative effort between UMMS and the State University of New York (SUNY) to develop two components of the academic detailing program. The first part consists of an interactive website, designed to bring the content of the academic detailing program to the entire state of New York. The second part consists of a face-to-face outreach efforts interacting with prescribers who serve a large number of Medicaid patients. To prepare for these interactions, staff from both UMMS-CPS and SUNY Upstate Medical University participated in a comprehensive, three-day training program run by Harvard University.



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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