

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

1-2 Drug Watch

New to Market
 New Generics
 New FDA-approved Indications
 New Formulations & Dosages

2 Clinical Notes

3 Advisories
 3 From the Hill
 Federal
 State

4 Pipeline

4 Noteworthy
 4 What's New at UMMS?

At a Glance



Noteworthy

A retrospective cohort of clopidogrel and proton pump inhibitors



What's New at UMMS?

UMMS CPS hosts the Residency Learning Systems training

New Generics

- **Stavudine (Zerit®)**
 Approved: 12/29/2008
 Launched: TBD
- **Lamotrigine (Lamictal®)**
 Launched: 1/2009*
- **Levetiracetam (Keppra®)**
 Launched: 1/2009*
- **Sumatriptan injection (Imitrex®)**
 Launched: 2/2009*
- **Sumatriptan tablet (Imitrex®)**
 Launched: 2/2009*
- **Topiramate (Topamax®)**
 Approved: 3/27/2009
 Launched: 3/27/2009
- **Mixed Amphetamine Salts (Adderall XR®)†**
 Launched: 4/2009

*Date represents when products became available from multiple sources

†Shire Pharmaceuticals authorized generic, 180-day exclusivity

Information available at www.fda.gov/cder/ogd/

Drug Watch



Savella® (milnacipran)

Approved: 1/14/2009
 Manufacturer: Cypress Bioscience, Inc.
 Formulation: Oral tablet
 Cost (AWP): Unavailable

Milnacipran is a selective serotonin norepinephrine dual reuptake inhibitor approved for the management of fibromyalgia. Effectiveness was evaluated in two placebo-controlled studies utilizing a composite outcome of syndrome response incorporating an assessment of pain, physical function, and patient's global assessment of disease. Milnacipran use resulted in a statistically greater percentage of syndrome responders, when compared to placebo. In one trial, 33 percent of patients treated with either milnacipran 100 mg or 200 mg were syndrome responders compared to 17 percent with placebo.

The recommended initial dose is 12.5 mg, increased to 100 mg/day, in divided doses (50 mg/day in renal insufficiency), over one week. The total daily dose may be increased to 200 mg/day based on individual response. Milnacipran is available as 12.5 mg, 25 mg, 50 mg, and 100 mg tablets.

Milnacipran is contraindicated in patients taking monoamine oxidase inhibitors (MAOI) concurrently, within 14 days of taking an MAOI, or those with narrow angle glaucoma. Milnacipran, expected to be available by mid 2009, is the third FDA-approved treatment for fibromyalgia, joining Cymbalta® (duloxetine) and Lyrica® (pregabalin).



Uloric® (febuxostat)

Approved: 2/13/2009
 Manufacturer: Takeda, Inc.
 Formulation: Oral tablet
 Cost (AWP): \$5.40/tablet

Febuxostat is a selective xanthine oxidase inhibitor approved for the chronic management of hyperuricemia in patients with gout. It is not recommended for use in patients with asymptomatic hyperuricemia.

Compared to allopurinol, treatment with febuxostat 80 mg or 120 mg results in more patients achieving a serum urate (SUA) <6.0 mg/dL ($P \leq 0.05$). In a six-month comparison of allopurinol and febuxostat, treatment with 80 mg of febuxostat resulted in more patients achieving SUA <6.0 mg/dL ($P < 0.001$) while treatment with 40 mg of febuxostat demonstrated comparable efficacy to allopurinol. However, in clinical trials, febuxostat did not reduce the need for treatment of acute flares when compared to allopurinol.

Treatment with febuxostat is initiated at a dose of 40 mg once daily. The dose may be increased to 80 mg daily if the patient's SUA remains above 6.0 mg/dL after two weeks. Due to the risk for abnormal liver function tests, it is recommended to assess liver function periodically during treatment.

Febuxostat joins other urate lowering therapies such as allopurinol and probenecid, but offers the convenience of once-daily administration and no need for renal dosing. It represents the first new gout treatment to be approved in 40 years.

New FDA-Approved Indications

- **PegIntron™ (peginterferon alfa-2b)**
Approved on 12/11/2008. Peginterferon alfa-2b is indicated for the treatment of chronic hepatitis C, with compensated liver disease previously untreated with interferon alpha, in patients ages 3 to 17 in combination with ribavirin.
- **Reclast® (zoledronic acid)**
Approved on 12/19/2008. Zoledronic acid is indicated to increase bone mass in men with osteoporosis.
- **Symbicort® (budesonide/formoterol)**
Approved on 2/27/2009. Budesonide/formoterol is indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease.
- **Copaxone® (glatiramer acetate for injection)**
Approved on 2/27/2009. Glatiramer acetate is indicated for the treatment of the first episode of multiple sclerosis in patients who also have magnetic resonance imaging findings of the disease.

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

New Formulations and Dosages

- **Avinza® (extended release morphine sulfate)**
45 mg and 75 mg capsules
Approved: 12/18/2008
- **Synvisc-One™ (hylan G-F 20)**
6 ml single intra-articular injection
Approved: 2/2/2009
- **Apidra® (insulin glulisine [rDNA origin] injection)**
SoloSTAR® 100 units/ml prefilled disposable insulin pen
Approved: 2/24/2009



Clinical Notes

Psoriatic Arthritis Treatment with an Emphasis on Biological Agents—May 2008

2008 Recommendations of the American Academy of Dermatology: Selected Key Points

- The American Academy of Dermatology released clinical practice guidelines for the treatment of psoriatic arthritis (PsA) with an emphasis on the use of biological agents (adalimumab, etanercept, and infliximab). The authors based their current recommendations on clinical evidence obtained through a MEDLINE database search spanning from 1990 to 2007.
- For mild PsA, adequate symptom relief can be achieved with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or local intra-articular injections of corticosteroids. Neither treatment is capable of inhibiting the development of structural joint damage.
- Moderate to severe PsA requires more potent therapy with disease-modifying antirheumatic drugs (DMARDs), tumor necrosis factor (TNF)-alpha inhibitors, or a combination of both.
- Data supporting the efficacy of methotrexate are inadequately powered to assess clinical benefit; however, it is frequently used as the primary DMARD in PsA due to the demonstrated efficacy in treating both skin and joint involvement and relative low cost.
- The potential importance of TNF-alpha inhibitors in the pathophysiology of PsA is underscored by the observation of elevated levels of TNF-alpha in the synovium, joint fluid, and skin of patients with PsA.
- The efficacy of DMARDs appears to be less than that of the TNF-alpha inhibitors; however, head-to-head studies are lacking to either support or refute this impression.
- There is convincing clinical and radiographic evidence supporting the efficacy of adalimumab regardless of whether or not methotrexate was used in combination. The response rate showed an American College of Rheumatology Criteria-20 (ACR-20) of 58 percent at week 12.
- Demonstrating similar efficacy as adalimumab, etanercept had an ACR-20 score of 59 percent at week 12; infliximab's score was 58 percent at week 14.
- TNF-alpha inhibitors are associated with potential long-term cost savings and long-term benefits, including reduced need for joint replacement surgery, reduced demands on medical, nursing, and therapy services, reduced needs for concomitant medications, improved quality of life, and increased life expectancy.
- Summary of final recommendations:
 - In mild PsA, NSAIDs or intra-articular injections of corticosteroids are recommended for symptom relief.
 - Methotrexate, TNF-alpha inhibitors, or a combination of both is considered first-line treatment for moderate-to-severe active PsA.
 - Based on the ACR-20 clinical efficacy data of the TNF-alpha inhibitors, all three FDA-approved agents are approximately equivalent.
 - Selection between TNF-alpha inhibitors is individualized based on the degree and severity of cutaneous involvement and safety concerns associated with therapy.

Advisories

Zonegran® and Metabolic Acidosis

On 2/23/09, the FDA determined treatment with Zonegran® (zonisamide), used for the treatment of partial seizures, can cause metabolic acidosis in some patients, especially younger patients. The FDA recommends that prescribers measure serum bicarbonate levels before initiating therapy and periodically thereafter. Zonisamide-induced metabolic acidosis can occur at anytime, but the risk appears greatest early in treatment and with higher doses. Patients with predisposing risk factors, including renal disease, severe respiratory disorders, diarrhea, or a ketogenic diet, are at higher risk. If metabolic acidosis develops and persists, consideration should be given to reducing or discontinuing therapy. If therapy is continued, alkali treatment should be

administered. The FDA is currently working with the makers of zonisamide to revise the product labeling to reflect this new safety information.

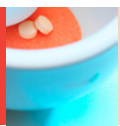
Boxed Warning for Metoclopramide

On 2/26/2009, the FDA required the addition of a boxed warning to the label of metoclopramide regarding risks associated with high-dose, long-term therapy. The development of tardive dyskinesia (TD) has been linked to the duration of metoclopramide therapy and number of doses taken. A recent analysis suggests that the majority of patients who developed TD received metoclopramide for more than three months. The FDA reports that metoclopramide is the most common cause of drug-induced movement disorders and chronic use should be avoided, especially in the elderly and in women. In addition to a boxed warning, the FDA has required manufacturers to implement a risk evaluation and

mitigation strategy for metoclopramide.

Raptiva® pulled from the market

On 4/8/09, Genentech, the makers of the psoriasis drug Raptiva® (efalizumab), decided to pull the medication off the U.S. market. The decision comes six months after the drug's label was updated with warnings of links to the development of progressive multifocal leukoencephalopathy (PML), an often fatal brain infection. There have been three confirmed cases of PML in patients taking efalizumab. Genentech states that there are approximately 2,000 people in the U.S. currently receiving efalizumab and recommends these patients talk with their physicians before stopping treatment. The company also states that no new prescriptions should be written for efalizumab. The drug will not be available after 6/8/09. Genentech made the decision to pull efalizumab off the market in conjunction with the FDA.



From The Hill

Federal

New Bill To Change Community Pharmacy Contracting

On 2/25/09, a bill known as the Community Pharmacy Fairness Act of 2009 was introduced in the House of Representatives. If passed, it would allow independent community pharmacies to negotiate the terms of their contracts with Pharmacy Benefits Managers (PBMs), similar to pharmacy chains. Current antitrust laws prevent this, and presently independent pharmacies are only offered take-it-or-leave-it contracts by the PBMs. It has been speculated that if contract negotiations were permitted, pharmacies would be better able to protect patients from changing formularies that place restrictions on treatment options. This would also help reduce prior-authorization difficulties found when patients request refills or formulary-restricted medications. The bill would also define independent pharmacies as those with less than 10 percent of market share in any prescription drug plan region, and less than one percent of market share in the U.S. The bill would place a market share cap of 25 percent in a Medicare Part D region for pharmacy negotiating pools.

For additional information please visit www.ncpanet.org/media/releases/2009/fairnessact.php.

State

Massachusetts: On 1/15/09, the Collaborative Drug Therapy Management (CDTM) practice bill became law in Massachusetts (Mass.), the 44th state to do so. States that already allow CDTM have noted increases in patient safety and health, reductions in medication errors and general health care costs, fewer emergency room visits, and improvements in patients' quality of life. Based upon a written protocol with the physician, the activities of the pharmacist may include the authorization to implement, modify, discontinue, or administer drug therapy, as well as permission to order appropriate laboratory tests required to monitor drug therapy. A pharmacist may also be permitted to order refills for up to a 30-day supply and administer immunizations to adult patients. Pharmacists practicing CDTM in Mass. must have earned a Pharm. D. or completed five years of experience as a licensed Pharmacist. They also need to have at least \$1,000 of professional liability insurance and have completed at least five additional contact hours or 0.5 continuing education units in an area related to CDTM.

For additional information please visit <http://www.masspharmacists.org/displaycommon.cfm?an=1&subarticlenbr=27>.

Pipeline

Multaq® (dronedaron)

Dronedaron (Multaq®), an antiarrhythmic agent under investigation by Sanofi-Aventis for the treatment of atrial fibrillation, has a pharmacologic profile similar to that of amiodarone. However, it lacks the iodine group thereby reducing the risk of thyroid and pulmonary complications.

Results from the ATHENA trial (NEJM. 2009;360:668) showed that dronedaron significantly reduced the risk of cardiovascular hospitalization and death (24%, $P < 0.001$), cardiovascular death (29%, $P = 0.03$), and arrhythmic death (45%, $P = 0.01$) when compared to placebo. Sanofi-Aventis submitted an NDA for dronedaron in July 2008, and the FDA has granted the application priority review.

Ustekinumab

Ustekinumab, developed by Centocor, Inc., is a human monoclonal antibody seeking approval for the treatment of moderate-to-severe plaque psoriasis. It works via a novel mechanism targeting the cytokines interleukin (IL)-12 and IL-23. A Phase III study comparing ustekinumab to Enbrel® (etanercept) showed that ustekinumab resulted in a significantly greater number of patients achieving at least a 75 percent reduction in psoriasis, as evaluated with the Psoriasis Area and Severity Index.

On 12/19/08, the FDA issued a Complete Response Letter for its Biologics License Application that included a request for a Risk Evaluation and Mitigation Strategy, and specifically the development of a Medication Guide.

Noteworthy

Risk of Adverse Outcomes Associated With Concomitant Use of Clopidogrel and Proton Pump Inhibitors Following Acute Coronary Syndrome

Proton pump inhibitors (PPIs), are commonly used to reduce the risk of gastrointestinal bleeding in patients receiving antiplatelet therapy following hospitalization for acute coronary syndrome (ACS), but they may reduce the inhibitory effects on platelet aggregation observed with clopidogrel.

A recent study followed 8,205 patients hospitalized for ACS who received clopidogrel monotherapy or in combination with a PPI upon discharge. Researchers observed an increased risk of death or rehospitalization for ACS with the combination compared to clopidogrel alone (29.8% versus 20.8%, respectively; adjusted odds ratio [AOR], 1.25; 95% confidence interval [CI]: 1.11-1.41). Secondary outcomes were also higher with combination therapy: hospitalizations for recurrent ACS (14.6% versus 6.9%; AOR, 1.86; 95% CI, 1.57-2.20) and revascularization (15.5% versus 11.9%; AOR, 1.49; 95% CI, 1.30-1.71).

The results of this study bear the limitations of all observational studies; however, support previous findings that PPIs inhibit the antiplatelet effects of clopidogrel. The most recent recommendation from the American Heart Association is that patients who are currently taking these medications should not change their medication regimen unless advised by a healthcare provider.

Ho PM, et al. JAMA. 2009;301(9):937-944.

What's New at UMMS?

On March 27, 2009, Clinical Pharmacy Services (CPS) hosted an all-day training at the Medical School, for directors and preceptors of accredited pharmacy residency programs across New England. With more than 50 participants from more than ten local programs, the event highlighted the core components of the Residency Learning System (RLS). The American Society of Health-Systems Pharmacists (ASHP) sponsors RLS, a systems-based approach to residency training, including mentorship, assessment, and program design. RLS is required of all training programs accredited by ASHP. Annually, CPS trains three managed care residents and up to two outcomes research fellows through our accredited residency and fellowship programs. Guest speaker David Warner led the group through hands-on exercises and problem-based discussions on RLS.

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 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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