

CPS Insider is produced by the University of Massachusetts Medical School's Clinical Pharmacy Services division and distributed to our clients quarterly.

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What's New at UMass Medical School?
CPS Optimizes Pharmacotherapy for Patients with Acquired Brain Injury

New Generics

- **Budesonide capsules (Entocort® EC)**
Launched: 6/23/11
- **Ketoconazole foam 2% (Extina®)***
Launched: 8/30/11
- **Levonorgestrel 90 mcg/ethinyl estradiol 20 mcg tablets (Lybrel®)**
Approval Date: 6/6/11
Launch Date: TBD
- **Levonorgestrel 0.15 mg/ethinyl estradiol 0.03 mg and ethinyl estradiol 0.01 mg tablets (Seasonique®)†**
Launched: 7/28/11
- **Oxymorphone HCl extended release tablets (Opana® ER)‡**
Launched: 7/15/11

* Perrigo Co. has 180-day market exclusivity.

† Teva Pharmaceuticals launched an authorized generic.

‡ Actavis Pharmaceuticals has launched generic oxymorphone HCl ER 7.5 mg and 15 mg. Watson Pharmaceuticals is expected to launch oxymorphone HCl ER 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg in September 2012.

Drug Watch



Arcapta™ (indacaterol)

Approved: 7/1/2011

Mfr: Novartis Pharmaceuticals

Formulation: Inhalation Powder

Cost (AWP): \$196/30 days

Arcapta™ Neohaler™ (indacaterol), a long-acting β_2 -adrenergic agonist (LABA), is approved as a maintenance bronchodilator for patients with chronic obstructive pulmonary disease (COPD), including emphysema and chronic bronchitis. Indacaterol is formulated as a 75 mcg capsule approved for once daily oral inhalation through the Neohaler™ device.

Three dose-ranging trials demonstrated no clear difference in forced expiratory volume in one second (FEV1) between indacaterol 75 mcg daily and higher doses (150 mcg, 300 mcg, and 600 mcg daily). Six double-blind, randomized, controlled trials (N=5,474) compared indacaterol in doses 75 mcg and higher to placebo and/or an active control (salmeterol, formoterol, or tiotropium) in patients with COPD. The primary efficacy endpoint for all six trials was based on the 24-hour postdose trough FEV1 at 12 weeks. Of these six trials, only two trials (N=641) evaluated the efficacy of indacaterol at the FDA-approved dose of 75 mcg daily. Results from these two trials demonstrated a mean difference in trough FEV1 of 130 mL between indacaterol and placebo at 12 weeks ($P<0.001$).

Common adverse reactions include cough, nasopharyngitis, and headache. Indacaterol has the same boxed warning as other LABAs for increased asthma-related death. Although not approved for asthma, indacaterol has the advantage of once daily dosing when compared to other LABAs dosed twice daily.



Potiga™ (ezogabine)

Approved: 6/10/2011

Mfr: Valeant Pharmaceuticals

Formulation: Tablet

Cost (AWP): Unavailable

Potiga™ (ezogabine) is a potassium channel opener indicated as add-on therapy for partial-seizures in adults ages 18 and older. Ezogabine may stabilize the resting membrane potential and lower brain excitability by facilitating the action of neuronal KCNQ channels. It is initiated at 100 mg three times daily and increased by 50 mg per dose at weekly intervals to a maintenance dose of 200 mg to 400 mg three times daily.

In three randomized trials (N=1,239) comparing ezogabine to placebo, one primary endpoint required by the FDA was the median percent reduction in monthly total partial-seizure frequency following 18 weeks of treatment. The RESTORE 1 trial showed a greater reduction in median monthly total partial-seizure frequency with ezogabine 1,200 mg daily compared to placebo (44.3 versus 17.5 percent, $P<0.001$). A dose-ranging study showed a greater median reduction in monthly total partial-seizure frequency from baseline for ezogabine 600 mg, 900 mg, and 1200 mg daily versus placebo (23, 29, and 35 versus 13 percent, $P<0.001$ for all).

Common adverse reactions include dizziness, somnolence, and fatigue. The FDA requires a REMS for ezogabine due to the risk of acute urinary retention. As the first potassium channel opener indicated as an adjunct for partial-seizures, it will likely compete with Lyrica® (pregabalin) and Keppra® (levetiracetam) as adjuncts for partial-seizures. Ezogabine is anticipated to be available at the end of the year after the DEA has evaluated its abuse potential and determined a controlled substance schedule.

New FDA-Approved Indications

- **Botox® (onabotulinumtoxinA)**
On Aug. 24, 2011, Botox® (onabotulinumtoxinA) was approved for the treatment of urinary incontinence resulting from detrusor overactivity in adults with neurologic conditions (e.g., spinal cord injury, multiple sclerosis) and with inadequate response or intolerance to an anticholinergic medication. In addition, onabotulinumtoxinA is indicated for the treatment of blepharospasms associated with dystonia, cervical dystonia, migraine prophylaxis, severe axillary hyperhidrosis, strabismus, and upper limb spasticity. Previously, no options were available for patients intolerant to anticholinergics.
- **Omnitrope® (somatropin)**
On July 22, 2011, Omnitrope® (somatropin) was approved for the treatment of pediatric patients with growth failure associated with Turner Syndrome. In addition, somatropin is indicated for the treatment of children with growth failure due to growth hormone deficiency, Prader-Willi Syndrome, Small for Gestational Age, and Idiopathic Short Stature. Other somatropin formulations indicated for growth failure associated with Turner Syndrome include Genotropin®, Humatrope®, Norditropin®, and Nutropin®.
- **Pegasys®/Copegus® (peginterferon alfa-2a/ribavirin)**
On Aug. 22, 2011, Pegasys®/Copegus® (peginterferon alfa-2a/ribavirin) was approved for the treatment of hepatitis C in children and adolescents ages 5 to 17 who have compensated liver disease and no prior history of interferon alpha therapy. PegIntron®/Rebetol® (peginterferon alfa-2b/ribavirin) is approved for the treatment of hepatitis C in children ages 3 and older with compensated liver disease.

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

New Formulations and Dosages

- **Lupron Depot-Ped® (leuprolide acetate)**
11.25 mg and 30 mg IM injection
Approved: 8/15/2011
- **Orencia® (abatacept)**
125 mg/mL SC injection
Approved: 7/29/2011
- **Zyclara® (imiquimod)**
2.5% cream
Approved: 7/19/2011



Clinical Notes

Pharmacotherapy for the Treatment of Acute Bipolar II Depression: Current Evidence from the Journal of Clinical Psychiatry

In March 2011, Swartz et al published a review in the *Journal of Clinical Psychiatry* citing the need for an update on treatment guidelines for Bipolar (BP) II Depression. The authors state that earlier treatment guidelines have few specific recommendations for BP II, leading clinicians to treat BP II depression based primarily on trials for BP I. Additionally, the authors explain that patients with BP II depression can present with both hypomanic and depressive symptoms resulting in more “mixed” episodes throughout the course of illness, alluding to the need for evidence-based treatment options specific to this population. The American Psychiatric Association (APA) last published a guideline for the treatment of BP depression in 2002, followed by a guideline watch with pharmacotherapy updates in 2005. For the treatment of BP depression, the APA provides evidence to support the use of lithium, lamotrigine, and adjunctive therapy with paroxetine. The guideline watch provided updated evidence for acute BP I depression treatment to include an olanzapine and fluoxetine fixed combination, quetiapine, and lamotrigine. Both of these guidelines include limited trials that are specific to BP II depression.

The Swartz review includes 21 studies, 90 percent of which were published after 2006, that evaluated quetiapine, lamotrigine, lithium, antidepressants, pramipexole, modafinil, and valproate. Quetiapine was evaluated in a post hoc analysis of data from two combined, multicenter, randomized, double-blind, placebo-controlled studies (BOLDER I and II; N=321) in patients with BP II.

Patients receiving quetiapine 300 mg or 600 mg daily compared to placebo demonstrated greater mean reduction in Montgomery-Asberg Depression Rating Scale scores (17.1 and 17.9 versus 13.3 points) and remission rates (39.3 and 37.7 versus 20.4 percent) after eight weeks (P-values not reported). BOLDER I and II provide evidence for the use of quetiapine as a first-line treatment option.

In a combined analysis of five double-blind, placebo-controlled trials, lamotrigine was found to have a modest advantage versus placebo in patients with BP II depression. A meta-analysis and meta-regression analysis of the same studies showed that lamotrigine was “superior” versus placebo in patients with Hamilton Depression Rating Scale (HDRS) scores greater than 24 (P-value not reported). A HDRS score equal to or greater than 23 is indicative of very severe depression. These studies provide evidence to support the use of lamotrigine as a preferred second-line agent for treatment of BP II depression. Lithium, pramipexole, and certain SSRIs are currently recommended as other second-line agents, but data supporting their efficacy is often based on lower quality evidence. Both valproate and modafinil use in BP II depression are not recommended due to inadequate data.

This review provides an update for the treatment of patients with acute BP II depression, as recommendations are based on new trials since the last guideline update. Additional randomized, controlled trials focusing on acute and maintenance treatment of BP II depression with longer follow-up are necessary to improve the quality of evidence used to guide clinical decision making.

Swartz HA, Thase ME. Pharmacotherapy for the treatment of acute bipolar II depression: current evidence. *J Clin Psychiatry*. 2011;72(3):356-366.

Advisories

FDA Action Due to Risk Associated with Avandia

On May 19, 2011, the FDA announced that Avandia® (rosiglitazone), Avandamet® (rosiglitazone/metformin), and Avandaryl® (rosiglitazone/glimepiride) will be removed from retail pharmacy shelves in November due to the increased risk of heart attack. It has been estimated that between 66,000 and 200,000 patients treated with rosiglitazone have experienced heart problems, leading to death in some patients, while taking the agent. By Nov. 18, 2011, the FDA will require practitioners to be certified to prescribe rosiglitazone-based products. Rosiglitazone will be available only to patients who meet all of the following criteria:

- Can be treated safely with the agent
- Have blood glucose levels that cannot be controlled with other drugs
- Prefer rosiglitazone to other agents after being informed of the risks.

In addition, rosiglitazone prescriptions must be filled through mail order pharmacies.

Long-term Use of High-Dose Fluconazole Associated with Birth Defects

On Aug. 3, 2011, the FDA warned against pregnant women using long-term, high-dose Diflucan® (fluconazole), 400 mg to 800 mg daily. Several published case reports describe the development of birth defects with the use of fluconazole in the first trimester. Exposed infants can present with short, broad heads; abnormal development of the skullcap; cleft palate; and congenital heart disease. The birth defects do not appear to be associated with a single, low dose of fluconazole 150 mg, typically used for the treatment of vaginal candidiasis. The pregnancy category for fluconazole has been reclassified from C to D for all therapeutic indications except for vaginal candidiasis, which remains category C. Health care providers should inform patients with regard to the fetal risk linked to high-dose fluconazole.

High Doses of Citalopram May Increase the Risk of QT Prolongation

On Aug. 24, 2011, the FDA alerted health care providers against prescribing citalopram in doses greater than 40 mg daily, which can prolong the QT interval in a dose-dependent manner and lead to a fatally abnormal heart rhythm such as Torsade de Pointes. The risk of QT prolongation is increased in patients with underlying heart conditions, such as congestive heart failure and bradyarrhythmias, and in patients predisposed to low blood levels of potassium and magnesium. Additionally, citalopram should not be used in patients with congenital long QT syndrome. The Dosage and Administration sections of the prescribing information for citalopram has been revised to reflect the new dose recommendation due to the risk of QT prolongation and inadequate evidence to support efficacy at doses greater than 40 mg daily. Lexapro® (escitalopram), may also cause QT prolongation but does not carry the same FDA warning as citalopram. The maximum recommended dose for escitalopram is 20 mg daily.

From The Hill

Federal

Drug Shortages in the U.S. Health Care System

The U.S. health care system has experienced recent drug shortages, primarily with intravenous chemotherapeutic agents and anti-infectives, but also common outpatient generic medications including metformin, amphetamine mixed salts, and oxycodone formulations. This shortage is an extension of a problem that began in 2010. Currently, 200 medications are listed in short supply, a number that has tripled in the past five years. This scarcity is driven by issues related to quality and manufacturing, delays and capacity, discontinuations, and supplies of raw material. The shortage has resulted in increased medication prices and limited patient access to certain medications. On Sep. 26, 2011, the FDA held a meeting with trade groups, physician organizations, drug manufacturers, group purchasing organizations, distributors, and patients to discuss solutions for the shortage. Proposed solutions include requiring manufacturers to give early warnings of potential shortages and creating a national stockpile of drugs in short supply through a nonprofit organization. For managed care entities, this shortage may lead to increased coverage of nonformulary and branded medications to replace generics in short supply.

State-Controlled Health Insurance Exchanges

State-based health insurance exchanges (HIX) will allow uninsured individuals and small businesses to purchase private health insurance plans in a competitive marketplace as of 2014. States can receive federal funding to develop their own exchanges or accept a federally mandated version designed by the Health and Human Services (HHS) as part of the Affordable Care Act (ACA). HHS has awarded \$185 million to the District of Columbia and 13 states with approved HIX legislation. With their own HIX initiatives, states can negotiate prices and determine parameters for plan qualification. Texas and Montana are taking steps to avoid the federal mandate, but South Carolina, Kansas, and Oklahoma have rejected federal dollars. Massachusetts and Utah established exchanges prior to the ACA. The Health Connector, which runs the Massachusetts HIX, and the Blue Cross Blue Shield Foundation are developing an online toolkit to assist other states in establishing their HIX. A federally mandated HIX would require HHS to assume responsibility for multiple exchanges. In preparation, HHS gathered officials from the District of Columbia and 46 states to propose HIX models with varying federal-state participation. One proposal requires states to control consumer affairs and HHS to determine member eligibility and enrollment.

Pipeline

Dapagliflozin

Dapagliflozin, a sodium-dependent glucose co-transporter 2 inhibitor, is currently being evaluated for the treatment of type 2 diabetes. In an extension of a 52-week, Phase III randomized, controlled trial, treatment with dapagliflozin added to metformin resulted in sustained HbA1c reduction at 104 weeks compared to baseline (-0.32 percent, 95 percent CI -0.42 to -0.21). On July 19, 2011, an FDA advisory committee voted 9-6 against recommending approval of dapagliflozin citing safety concerns. Pooled data from 11 Phase III trials showed nine cases each for bladder and breast cancers reported in patients receiving dapagliflozin compared to one case of each cancer in the placebo group (0.16 versus 0.03 percent, $P=0.15$; 0.4 versus 0.09 percent, $P=0.27$; respectively). An FDA response is expected by Oct. 28, 2011.

Safinamide

Safinamide, a monoamine oxidase B inhibitor being studied as adjunctive therapy in Parkinson's disease (PD), decreases dyskinesia by suppressing dopamine reabsorption and glutamate release. A Phase III extension study evaluated safinamide as adjunct therapy to levodopa in advanced stage PD. At 24 months, treatment with safinamide 50 mg and 100 mg resulted in an increase in "ON" time, or period of best motor function, versus placebo (1.01 and 1.18 versus 0.34 hours, $P=0.0031$ and $P=0.0002$, respectively). Two ongoing Phase III trials, MOTION and SETTLE, are currently evaluating the safety and efficacy of safinamide, with MOTION expected to have an 18-month extension trial. A new drug application submission is planned for 2012.

Noteworthy

Comparative Effectiveness Research in Health Care Reform

In 2009, the Obama administration sponsored comparative effectiveness research (CER) after the enactment of the Patient Protection and Affordable Care Act. The Act established the Patient-Centered Outcomes Research Institute (PCORI), which will receive approximately \$550 million per year to fund and disseminate data from CER studies. This type of study is used to determine how medical initiatives in development compare to current standards of care. PCORI will also attempt to elevate the role of CER in the health care system.

The Agency for Healthcare Research and Quality (AHRQ) Effective Health Care (EHC) Program currently manages a library of CER reviews dating back to 2005. The CER reviews, using study data from new or existing research, are developed in collaboration with researchers and academic institutions. A recent 2011 CER review evaluates oral medications used for the treatment of type 2 diabetes. The library of CERs is available at <http://effectivehealthcare.ahrq.gov/>.

To support translational CER for pharmacy and therapeutics committees and other drug policy decision makers, the Academy of Managed Care Pharmacy and the University of Arizona are hosting AHRQ grant-supported educational sessions at select conferences focused on the use of CERs in making coverage decisions. Other educational tools will be offered online and through publications.

Managed care pharmacists are often directly responsible for formulary decisions based on limited information on drug cost, safety, and efficacy. The increased availability of CERs over time is likely to further strengthen robust evidence-based coverage decisions.

Production Staff

Editor-in-Chief

Karen Lee, Pharm.D., BCPS
Director for Professional Development
UMMS Clinical Pharmacy Services

Managing Editor

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UMMS Clinical Pharmacy Services

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an SXC company

Contributing Editors

Sarah Mordkovich, Pharm.D.
Clinical Pharmacy Resident
UMMS Clinical Pharmacy Services

Corey O'Brien, Pharm.D.
Clinical Pharmacy Resident
UMMS Clinical Pharmacy Services

Additional Contributors

Deanna Joubert, Pharm.D.
Clinical Consultant Pharmacist
UMMS Clinical Pharmacy Services

Jennifer Sacco, Pharm.D. Candidate
Najma Saleem, Pharm.D. Candidate
Nicole Trask, Pharm.D. Candidate
UMMS Clinical Pharmacy Services



What's New at UMass Medical School?

The Massachusetts Rehabilitation Commission, MassHealth, and UMass Medical School, offer two acquired brain injury (ABI) waivers: one with residential habilitation for patients in a community setting requiring supervision (ABI-RH) and one for patients who can live at home or someone else's home (ABI-N). This program is available to Medicaid-eligible patients who have experienced an ABI at age 22 or older, have resided in a nursing facility or chronic rehabilitation center for at least 90 days, and have service needs limited to \$194,486 per year for ABI-RH and \$99,890 per year for ABI-N. Causes of ABI include stroke, brain trauma, infections (e.g., encephalitis),

brain tumor, or anoxia. These patients struggle with administering their medications and remembering complex regimens.

At UMass Medical School's Clinical Pharmacy Services (CPS), pharmacists visit patients in home and community settings to provide medication reviews and recommendations and to help minimize care costs. For example, CPS pharmacists visited a patient home in early 2011 and identified a case of drug-induced sedation. CPS recommended therapy modification that improved the member's mental status and quality of life, while lessening the cost of care. As a new initiative, CPS also provides medication reviews for patients newly enrolled into the waiver.

Who We Are and What We Do



The University of Massachusetts Medical School's Clinical Pharmacy Services is a comprehensive prescription drug management program developed in 1999 as part of the Medical School's Commonwealth Medicine division, primarily to provide drug utilization review for Massachusetts Medicaid. Today, we bring 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, pharmaco-economic modeling, drug utilization review, medication therapy management, clinical call center support, and provider/patient education. The *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 we welcome your suggestions for improvement.



University of Massachusetts Medical School
Clinical Pharmacy Services

UMass Medical School
333 South Street
Shrewsbury, MA 01545

Contact:

Timothy Cummins, M.B.A., RPh
Executive Director

Clinical Pharmacy Services

Tel: 774-455-3440

Fax: 877-208-7428

Website: www.umassmed.edu/cps

Email: Timothy.Cummins@umassmed.edu