

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

Clopidogrel-related deaths and acute MI; antidepressant efficacy



What's New at UMMS?

CPS collaborates with State University of New York (SUNY)

New Generics

- **Calcium acetate tablets (Phoslo®)**
Approved 1/30/2008
- **Cefuroxime axetil oral suspension (Ceftin®)**
Approved 2/5/2008
- **Alendronate sodium tablets (Fosamax®)**
Approved 2/6/2008
- **Pramipexole tablets (Mirapex®)**
Approved 2/19/2008
- **Calcium acetate gel caps (Phoslo®)**
Approved 2/26/2008

Drug Watch



Intelence® (etravirine)

Approved: 1/18/2008
 Manufacturer: Tibotec, Inc.
 Formulation: Tablet

Etravirine is an HIV-1 specific, non-nucleoside reverse transcriptase inhibitor (NNRTI) that binds directly to reverse transcriptase and blocks RNA-dependent and DNA-dependent DNA polymerase activities by causing a disruption of the enzyme's catalytic site. It is the first NNRTI found to be effective in patients with NNRTI resistant HIV strains.

Etravirine is FDA-approved for combination therapy with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients, who have evidence of viral replication and HIV-1 strains resistant to an NNRTI and other antiretroviral agents.

The recommended adult dose is 200mg twice daily following a meal. The most common adverse events are rash and nausea.

Etravirine is a substrate of CYP3A4, CYP2C9 and CYP2C19. Therefore, co-administration of etravirine with drugs that are substrates, inducers, or inhibitors of CYP3A4, CYP2C9 and CYP2C19 may alter the therapeutic effects of etravirine and/or the interacting drug.



Pristiq® (desvenlafaxine)

Approved: 2/29/2008
 Manufacturer: Wyeth, Inc.
 Formulation: Tablet

Desvenlafaxine succinate (DVS), or O-desmethyl-venlafaxine, is the major active metabolite of the serotonin-norepinephrine reuptake inhibitor venlafaxine. Unlike venlafaxine, DVS is not metabolized via the CYP450 pathway and has antidepressant efficacy comparable to venlafaxine ER.

DVS is FDA-approved for the treatment of major depressive disorder (MDD) in adults.

The recommended dose is 50mg once daily. Doses greater than 50mg/day do not confer any additional benefit.

As with all antidepressants, the FDA issued a black box warning of potential increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants for MDD.

The most common adverse events include nausea, somnolence, nervousness, anorexia, constipation and dry mouth.

Concomitant use with a monoamine oxidase inhibitor is contraindicated. Caution is advised when coadministered with other serotonergic drugs due to the risk of serotonin syndrome. DVS is not metabolized by the CYP450 pathway; therefore, it has minimal inhibition of CYP enzymes. It is eliminated primarily by phase 2 metabolism to form a glucuronide conjugated metabolite and by renal excretion of unchanged DSV.

New FDA-Approved Indications

- **Tysabri® (nazalimumab)**
Approved on 1/14/2008. Treatment of moderate to severe Crohn's disease with evidence of inflammation in patients who have failed conventional therapies.
- **Humira® (adalimumab)**
Approved on 1/18/2008. Treatment of moderate to severe chronic plaque psoriasis in adults who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate.
Approved on 2/21/2008. Management of signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years and older.
- **Welchol® (colesevelam)**
Approved on 1/18/2008. Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes.
- **Asmanex® (mometasone)**
Approved on 2/26/2008. Expanded approval for the maintenance of asthma in children 4 years and older.
- **Nexium® (esomeprazole)**
Approved on 2/28/2008. Expanded approval for the short-term treatment of GERD in children 1-11 years of age.

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

New Formulations and Dosages

- **Cialis® (tadalafil)**
2.5mg tablet (once daily dosing)
Approved 1/8/2008
- **Tektura HCT® (aliskiren/HCTZ)**
150/12.5, 150/25, 300/12.5, and 300/25mg tablets
Approved 1/18/2008
- **Simcor® (niacin/simvastatin)**
500/20, 750/20, 1,000/20mg extended-release tablets
Approved 2/15/2008
- **Nexium® (esomeprazole)**
10mg unit dose packet
Approved 2/27/2008

Clinical Notes

GUIDELINES FOR THE USE OF ANTIRETROVIRAL AGENTS IN PEDIATRIC HIV INFECTION - 2/2008

Initiating Therapy in Antiretroviral Naïve-Children: Selected Key Points

- Infants aged <12 months: Although controversial, the initiation of antiretroviral therapy (ART) is recommended regardless of clinical status, CD4 count, or viral load.
- Children ≥1 year of age: Initiate therapy if the CD4 threshold has been met (CD4 <25% for children aged 1 to <5 years and <350 cells/mm³ for children ≥5 years) or if the child has AIDS or significant symptoms.
- Children ≥1 year of age: Initiate therapy in children who are asymptomatic or have mild symptoms. Initiation of ART may be deferred in some patients. Specific recommendations are dependent upon patient age, CD4 count, and HIV RNA levels.

Additional Key Points

- Generally, a combination ART in treatment-naïve children contains 1 NNRTI + a 2-NRTI backbone or 1 PI + a 2-NRTI backbone. A 3-NRTI regimen, including zidovudine, abacavir, and lamivudine, is recommended only if a PI- or NNRTI-regimen cannot be used.
- Preferred NNRTI based regimens include efavirenz in combination with 2 NRTIs for children aged ≥3 years, or nevirapine in combination with 2 NRTIs for children aged <3 years or who require a liquid formulation.
- Preferred PI based regimens include lopinavir/ritonavir in combination with 2 NRTIs.

For additional information, please visit: <http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf>

GUIDELINES FOR THE USE OF ANTIRETROVIRAL AGENTS IN HIV-1 INFECTED ADULTS AND ADOLESCENTS - 1/2008

Recommendations for the Antiretroviral-Naïve Patient: Selected Key Points

Recommendations for "preferred" and "alternative" antiretrovirals have been revised as follows:

- Abacavir + lamivudine has been changed to a preferred 2-NRTI component in patients who have tested negative for HLA-B*5701
- Zidovudine + lamivudine has been changed to an alternative 2-NRTI component
- Ritonavir-boosted saquinavir has been changed to an alternative PI component.

The following components are no longer recommended: nelfinavir as a PI component, stavudine + lamivudine as 2-NRTI components and abacavir + zidovudine + lamivudine as a triple-NRTI combination.

Additional Key Points

- Generally, a combination ART regimen in treatment-naïve patients contains 1 NNRTI + 2 NRTIs or a single or ritonavir-boosted PI + 2 NRTIs.
- If therapy is initiated before drug resistance test results are available, consideration should be given to using a PI-based regimen since clinically significant resistance to PIs is less common vs. to NNRTIs.
- Long-term treatment interruption is not recommended unless in the context of a clinical trial.

For additional information, please visit: <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf>

Advisories

Bisphosphonates

On 1/7/08, the FDA issued an alert highlighting an association between severe musculoskeletal pain and bisphosphonate use. Severe musculoskeletal pain can present distinct from the acute phase response and may occur within days to years of initiating bisphosphonate therapy. Healthcare professionals should consider temporary or permanent drug discontinuation in patients who present with symptoms to avoid potential impairment.

Antiepileptics

On 1/31/08, the FDA issued an alert regarding the risk of suicidality in patients receiving antiepileptics following an analysis of various placebo-controlled studies in which patients receiving antiepileptic drugs had approximately double the risk of

suicidal behavior or ideation compared to patients receiving placebo. The increased risk was observed as early as one week and continued through 24 weeks. The risk was higher in patients treated for epilepsy compared to patients treated for psychiatric or other conditions. If the benefits of therapy outweigh the risks for any individual, the patient should be closely monitored for changes in behavior.

Chantix® (varenicline) and Tamiflu® (oseltamivir)

On 2/1/08 and 3/4/08, the FDA informed healthcare professionals and consumers of important revisions to the prescribing information for Chantix® and Tamiflu®, respectively. The changes resulted from reports of serious neuropsychiatric symptoms experienced by patients taking the products. Symptoms associated with both products have included abnormal behaviors and may have led to fatal

outcomes. For additional information regarding the individual products, please see the respective package inserts.

Tussionex® Pennkinetic® Extended-Release Suspension (hydrocodone and chlorpheniramine)

On 3/11/08, the FDA issued a public health advisory regarding the safe use of Tussionex® following reports of life-threatening and fatal respiratory depression. The product should not be administered more frequently than every 12 hours and should not be administered to children less than 6 years of age. Healthcare professionals and patients should be aware of the signs of hydrocodone overdose and should understand the importance of using a device that can accurately measure each dose of the product.



From The Hill

Federal

Bills Passed Related to Mental Health Parity

Both the House and Senate have passed bills related to insurance coverage for the treatment of mental illnesses. Both bills are related to mental health parity and specifically forbids health insurers from setting stricter limits on treatment or higher co-payments for mental health services than for other medical care benefits. A law passed in 1996 outlawed health plans from setting annual or lifetime dollar limits on mental health care that are lower than limits set for other services. However, many insurers currently have annual limits on mental health benefits, such as 30 doctor visits or 30 days of hospital care. Under this new legislation, these limits would not be allowed unless such limits were also set on the treatment of physical illnesses, such as cancer and diabetes mellitus. Many insurers and employer groups are in favor of the Senate bill; however many of these groups oppose the House bill which also applies to alcohol and drug abuse treatment.

For additional information, please visit: www.nytimes.com/2008/03/06/washington/06health.html

State

Massachusetts: Legislation has been introduced to promote cost containment, transparency, and efficiency in the delivery of quality health care. An amendment to the General Laws includes the implementation and promotion of a pharmacy academic detailing program. This evidence-based outreach and education program is designed to optimize the therapeutic and cost-effective utilization of prescription medication. Additionally, proposed legislation would ban all Pharma gifts to physicians, require all state physicians to adopt electronic records by 2015, and allow patients to choose nurse practitioners as their primary care providers. Public reviews of some insurance company efforts would also be required.

For additional information, please visit: www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=50754 and www.mass.gov/legis/laws/mgl/gl-111-toc.htm

Pipeline

Effient® (prasugrel)

Prasugrel is an oral antiplatelet agent that inhibits platelet activation and aggregation by blocking the P2Y₁₂ adenosine diphosphate receptor on the platelet surface. In February of 2008, the FDA granted the NDA priority review status for patients with acute coronary syndrome being managed with percutaneous coronary intervention. As a result, prasugrel may enter the market as soon as the third quarter of 2008. Initial evidence appears to suggest a net clinical benefit in favor of using prasugrel instead of Plavix® (clopidogrel). In a comparison trial of the agents, treatment with prasugrel resulted in a reduced combined rate of death from cardiovascular disease, nonfatal myocardial infarction, or nonfatal stroke at the expense of increased rates of serious and fatal bleeding.

Rendix® (dabigatran)

Dabigatran is a direct thrombin inhibitor currently being studied in trials for stroke prevention in atrial fibrillation, prevention of deep vein thrombosis (DVT) following hip or knee replacement surgery, acute DVT treatment, and secondary prevention of DVT. Preliminary results from an extensive thromboembolic disease clinical trial program are expected in early 2009. Dabigatran is administered orally and provides the benefit of a consistent anti-coagulation effect without the need for coagulation monitoring and dosage adjustment.

1. Ho M, et al. JAMA. 2008;299(5):532-539.

2. Kirsch I, et al. Plos Med. 2008 Feb;5(2):e45.

Noteworthy

Clopidogrel: Increased risk of adverse events within 90 days of cessation¹

According to a national cohort study by Ho et al, there was a higher incidence of death and acute myocardial infarction within 90 days of stopping clopidogrel in medically treated and percutaneous coronary intervention-treated patients with acute coronary syndrome. These study results are supported by similar previous findings of rebound-platelet activation associated with the discontinuation of long-term aspirin or heparin therapy. Further evaluation is needed to confirm the clustering of thrombotic events and the mechanism associated with this reported event.

Antidepressants: Below standards of clinical significance for use in depression²

Kirsch et al conducted a meta-analysis of published and unpublished clinical trials studying antidepressant(s) (i.e., fluoxetine, venlafaxine, nefazodone, paroxetine) vs. placebo and reporting a change in improvement scores. The trials support a score difference of 1.80 between drug and placebo using the Hamilton Rating Scale of Depression; however, this does not meet the score difference of 3.0 as defined as clinical significance by the National Institute for Clinical Excellence. Despite this modest benefit, efficacy of antidepressants when used for very severe depression may be attributed to a decline in placebo effectiveness rather than an increase in medication responsiveness. Results of the meta-analysis suggest that the efficacy of antidepressant therapy is below accepted criteria for clinical significance.

What's New at UMMS?

CPS' work with New York (NY) Medicaid has progressed rapidly over the past few months. We are in the process of developing programs for retrospective drug utilization review (RetroDUR), medication therapy management (MTM), and academic detailing. Commonwealth Medicine has developed a relationship with the State University of NY (SUNY) to help facilitate the roll-out of these programs. With our initial collaboration focused around RetroDUR case reviews, we have recently started development of an asthma MTM program. This program will utilize community pharmacists to educate and train patients on their disease state as well as the proper use of their medications. The creation of a comprehensive academic detailing physician education program has been stalled by the introduction of legislation in New York that may impact our ability to provide these services at a high level. We are currently awaiting the outcome of those discussions and the final language before moving forward.



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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