

P & T News

Published by the **Pharmacy and Therapeutics Subcommittee** of the University Hospital
Advisory Committee and the Department of Pharmaceutical Care

Volume 25 Number 4

Spring 2005

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SAFETY UPDATES: CELECOXIB AND ANTIDEPRESSANTS

During the past several months, new safety information regarding celecoxib and the use of antidepressants in children has been brought to the attention of healthcare providers. The new warnings for the use of these agents are summarized below.

Celecoxib

The Food and Drug Administration (FDA) has recently asked the manufacturers of all prescription and over-the-counter nonsteroidal anti-inflammatory drugs (NSAID), including celecoxib (Celebrex®), to revise the package insert to include a boxed warning to highlight the potential for increased cardiovascular (CV) events, as well as gastrointestinal bleeding. In addition, the FDA has also requested that the package insert for all NSAIDs be revised to include a contraindication for use in patients immediately post-operative from coronary artery bypass (CABG) surgery.

The data regarding celecoxib that prompted these conclusions include:

- In the National Cancer Institute's Adenoma Prevention with Celecoxib® (APC) trial in patients at risk for recurrent colon polyps, a two- to three-fold increased risk of serious adverse CV events was seen for Celebrex® compared to placebo after a mean duration of treatment of 33 months. There appeared to be a dose response relationship, with a hazard ratio of 2.5 for Celebrex® 200 mg twice daily and 3.4 for Celebrex® 400 mg twice daily for the composite endpoint of death from CV causes, myocardial infarction (MI), or stroke.
- In the nearly identical Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial, the APC results were not replicated. Based on preliminary, unpublished data presented by the investigators at the February 16-18, 2005, FDA meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee, the hazard ratio was 1.1 for celecoxib 400 mg once daily compared to placebo for the composite endpoint of death from CV causes, MI, or stroke. (Extensive data related to the cardiovascular safety of Celebrex® and other COX-2 selective and non-selective NSAIDs were presented at this Advisory Committee meeting. This information is available on the following website: <http://www.fda.gov/ohrms/dockets/ac/cder05.html#ArthritisDrugs>.)
- Another long-term controlled trial, the National Institute of Aging's Alzheimer's Disease Anti-Inflammatory Prevent Trial (ADAPT), compared Celebrex® 200 mg twice daily to placebo in patients at risk for Alzheimer's disease. Data are not yet available from this trial; however, a preliminary report released by NIH on December 20, 2004, (<http://www.nih.gov/news/pr/dec2004/od-20.htm>) suggested that no increased risk of serious adverse CV events was found for Celebrex® compared to placebo.



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- The only available data from a long-term comparison of Celebrex® to other NSAIDs come from the Celebrex® Long-Term Arthritis Safety Study (CLASS) in which Celebrex® 400 mg twice daily was compared to diclofenac and ibuprofen in approximately 8,000 patients with osteoarthritis. No differences were observed for serious adverse CV events between Celebrex® and the two NSAID comparators in this trial.
- In two short-term placebo-controlled clinical trials in patients immediately post-operative from CABG surgery, valdecoxib, another COX-2 selective NSAID, was associated with an approximately two-fold increased risk of serious adverse CV events compared to placebo. No data are available for Celebrex® in the post-CABG surgery population; however, pending receipt of further data, FDA has concluded that all NSAIDs, including Celebrex®, should be contraindicated in patients immediately post-operative from CABG surgery.

The FDA's recommendations for the use of celecoxib include:

- Physicians are encouraged to carefully weigh the potential benefits and risks of celecoxib versus other treatment options for the condition to be treated before a decision is made to use celecoxib. If celecoxib is selected for an individual patient, FDA encourages use of the lowest effective dose for the shortest duration consistent with individual patient treatment goals.
- Celecoxib should not be used in patients who are immediately post-operative from CABG surgery.

Based on marginal benefit outside the high-risk patient populations and increased risk for adverse cardiovascular effects, **at UIHC the prescribing of celecoxib is restricted to the following conditions:**

- **The patient has rheumatoid arthritis, osteoarthritis, or chronic pain AND is at high risk for GI bleeding, GI ulceration, or other bleeding problem (e.g., receiving oral or systemic corticosteroids, receiving anticoagulants, thrombocytopenia, greater than 70 years of age) with use of an NSAID AND the patient is not receiving proton pump inhibitor therapy AND the patient is not at high risk for a cardiovascular event.**
- **Chronic pain in a patient with thrombocytopenia or hemophilia.**
- **Therapy for familial adenomatous polyposis (FAP).**
- **Documentation of intolerance to two previous trials of different multisource (generically available) NSAIDs AND the patient is not at high risk for a cardiovascular event.**

Antidepressant Use in Children

In October 2004, the FDA issued a Public Health Advisory regarding suicidality in children and adolescents being treated with antidepressant medications. Since the original notice the FDA has modified the "black box" warning labeling changes to read:

Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Insert drug name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ... (See Warnings and Precautions: Pediatric Use)

Pooled analyses of short-term (4 to 16 weeks) placebo-controlled trials of 9 antidepressant drugs (SSRIs and others) in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders (a total of 24 trials involving over 4400 patients) have revealed a greater risk of adverse events representing suicidal thinking or behavior (suicidality) during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%. No suicides occurred in these trials.

This change in labeling applies to all brand and generic preparations of: Anafranil® (clomipramine), Asendin® (amoxapine), Aventyl® (nortriptyline), Celexa® (citalopram), Cymbalta® (duloxetine), Desyre® (trazodone), Elavil® (amitriptyline), Effexor® venlafaxine), Etrafon® (perphenazine/amitriptyline), Luvox® (fluvoxamine), Lexapro® (escitalopram), Limbitrol® (chlordiazepoxide/amitriptyline), Ludiomil® (maprotiline), Marplan® (isocarboxazid), Nardil® (phenelzine), Norpramin® (desipramine), Pamelor® (nortriptyline), Parnate® (tranylcypromine), Paxil® (paroxetine), Peveva® (paroxetine mesylate), Prozac® (fluoxetine), Remeron® (mirtazapine), Sarafem® (fluoxetine), Serzone® (nefazodone), Sinequan® (doxepin), Surmontil® (trimipramine), Symbyax® (olanzapine/fluoxetine), Tofranil® (imipramine), Tofranil-PM® (imipramine pamoate), Triavil® (perphenazine/amitriptyline), Vivactil® (protriptyline), Wellbutrin® (bupropion), Zoloff® (sertraline), and Zyban® (bupropion).

In addition, the FDA determined that a patient medication guide (MedGuide) must be given to patients with each prescription or refill to advise them of the risk and the precautions that can be taken. See Figure 1 for a template of the MedGuide.

Adapted From:

<http://www.fda.gov/cder/drug/infopage/celebrex/celebrex-hcp.htm> Accessed April 21, 2005

http://www.fda.gov/cder/drug/antidepressants/PI_template.pdf Accessed April 21, 2005

http://www.fda.gov/cder/drug/antidepressants/MG_template.pdf Accessed April 21, 2005

http://www.fda.gov/cder/drug/antidepressants/MDD_alldruglst.pdf Accessed April 21, 2005

FIGURE 1

**Medication Guide
About Using Antidepressants in Children and Teenagers**

What is the most important information I should know if my child is being prescribed an antidepressant?

Parents or guardians need to think about 4 important things when their child is prescribed an antidepressant:

1. There is a risk of suicidal thoughts or actions
2. How to try to prevent suicidal thoughts or actions in your child
3. You should watch for certain signs if your child is taking an antidepressant
4. There are benefits and risks when using antidepressants

1. There is a Risk of Suicidal Thoughts or Actions

Children and teenagers sometimes think about suicide, and many report trying to kill themselves. Antidepressants increase suicidal thoughts and actions in some children and teenagers. But suicidal thoughts and actions can also be caused by depression, a serious medical condition that is commonly treated with antidepressants. Thinking about killing yourself or trying to kill yourself is called suicidality or being suicidal.

A large study combined the results of 24 different studies of children and teenagers with depression or other illnesses. In these studies, patients took either a placebo (sugar pill) or an antidepressant for 1 to 4 months. No one committed suicide in these studies, but some patients became suicidal. On sugar pills, 2 out of every 100 became suicidal. On the antidepressants, 4 out of every 100 patients became suicidal.

For some children and teenagers, the risks of suicidal actions may be especially high. These include patients with

- Bipolar illness (sometimes called manic-depressive illness)
- A family history of bipolar illness
- A personal or family history of attempting suicide

If any of these are present, make sure you tell your healthcare provider before your child takes an antidepressant.

2. How to Try to Prevent Suicidal Thoughts and Actions

To try to prevent suicidal thoughts and actions in your child, pay close attention to changes in her or his moods or actions, especially if the changes occur suddenly. Other important people in your child's life can help by paying attention as well (e.g., your child, brothers and sisters, teachers, and other important people). The changes to look out for are listed in Section 3, on what to watch for.

Whenever an antidepressant is started or its dose is changed, pay close attention to your child.

After starting an antidepressant, your child should generally see his or her healthcare provider:

- Once a week for the first 4 weeks
- Every 2 weeks for the next 4 weeks
- After taking the antidepressant for 12 weeks
- After 12 weeks, follow your healthcare provider's advice about how often to come back
- More often if problems or questions arise (see Section 3)

You should call your child's healthcare provider between visits if needed.

FIGURE 1 (CON'T)

3. You Should Watch for Certain Signs if Your Child is Taking an Antidepressant

Contact your child's healthcare provider right away if your child exhibits any of the following signs for the first time, or if they seem worse, or worry you, your child, or your child's teacher:

- Thoughts about suicide or dying
- Attempts to commit suicide
- New or worse depression
- New or worse anxiety
- Feeling very agitated or restless
- Panic attacks
- Difficulty sleeping (insomnia)
- New or worse irritability
- Acting aggressive, being angry, or violent
- Acting on dangerous impulses
- An extreme increase in activity and talking
- Other unusual changes in behavior or mood

Never let your child stop taking an antidepressant without first talking to his or her healthcare provider. Stopping an antidepressant suddenly can cause other symptoms.

4. There are Benefits and Risks When Using Antidepressants

Antidepressants are used to treat depression and other illnesses. Depression and other illnesses can lead to suicide. In some children and teenagers, treatment with an antidepressant increases suicidal thinking or actions. It is important to discuss all the risks of treating depression and also the risks of not treating it. You and your child should discuss all treatment choices with your healthcare provider, not just the use of antidepressants.

Other side effects can occur with antidepressants (see section below).

Of all the antidepressants, only fluoxetine (Prozac®) has been FDA approved to treat pediatric depression.

For obsessive compulsive disorder in children and teenagers, FDA has approved only fluoxetine (Prozac®), sertraline (Zoloft®), fluvoxamine, and clomipramine (Anafranil®).

Your healthcare provider may suggest other antidepressants based on the past experience of your child or other family members.

Is this all I need to know if my child is being prescribed an antidepressant?

No. This is a warning about the risk for suicidality. Other side effects can occur with antidepressants. Be sure to ask your healthcare provider to explain all the side effects of the particular drug he or she is prescribing. Also ask about drugs to avoid when taking an antidepressant. Ask your healthcare provider or pharmacist where to find more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Revised 1/26/05

PHARMACY AND THERAPEUTICS SUBCOMMITTEE ACTIONS

DRUGS ADDED TO STOCK

HYDROMORPHONE

Extended-Release Tablets: 12 mg, 16 mg, 24 mg, 32 mg

This formulation of hydromorphone (Palladone® - Purdue) is indicated for the treatment of persistent, moderate to severe pain in patients requiring continuous, round-the-clock analgesia with a high-potency opioid for an extended period of time.

Note: The prescribing of Palladone® is restricted to the Palliative Care and Pain Services.

LANTHANUM CARBONATE

Tablets: 250 mg and 500 mg

Lanthanum Carbonate (Fosrenol® - Shire) is indicated to reduce serum phosphate levels in patients with end-stage renal disease.

PEGAPTANIB

Intravitreal Injection: 0.3 mg

Pegaptanib (Macugen® - Pfizer) is indicated for the treatment of neovascular age-related macular degeneration.

Note: The prescribing of pegaptanib is restricted to Ophthalmology.

RIFAXIMINE

Tablets: 200 mg

Rifaximine (Xifaxan® - Salix) is a non-absorbed oral antibiotic indicated for the treatment of traveler's diarrhea.

SODIUM FLUORIDE

Dentifrice: 1.1%

This dentifrice (PreviDent® 5000 Plus - Colgate) is indicated for once-daily application for prevention of dental caries to remineralize weakened teeth in at-risk patients.

PHARMACY AND THERAPEUTICS SUBCOMMITTEE ACTIONS

DRUGS ADDED TO STOCK (CON'T)

TINIDAZOLE

Tablets: 500 mg

Tinidazole (Tindamax® - Presutti) is an antiprotozoal drug indicated for the treatment of trichomoniasis, giardiasis, and amebiasis.

TRYPAN BLUE

Ophthalmic Solution: 0.06%

Trypan blue (Vision Blue® - D.O.R.C.) selectively stains connective tissue structures in the eye and is used for visualization during ophthalmologic surgery.

DELETED FROM STOCK

ALPROSTADIL (MUSE®) 1000 mcg URETHRAL SUPPOSITORIES

Deleted due to low use. Papaverine/phentolamine/alprostadil injection and alprostadil 500 mcg urethral suppositories are available.

AMPICILLIN CAPSULES AND ORAL SUSPENSION

Deleted due to low use. Amoxicillin is available.

BATHING ALCOHOL

Replaced with other disinfectants.

CASCARA SAGRADA ORAL SOLUTION

Deleted due to low use. Bisacodyl tablets and sennosides oral solution are available.

CONJUGATED ESTROGENS (PREMARIN®) 1.25 mg TABLETS

Replaced with 0.45 mg tablets.

CONJUGATED ESTROGENS 0.625 mg WITH MEDROXYPROGESTERONE 5 mg (PREMPRO®) TABLETS

Replaced with conjugated estrogens 0.3 mg with medroxyprogesterone 1.5 mg tablets.

DIDANOSINE (VIDEX®) ORAL POWDER

Deleted due to low use.

ETHINYL ESTRADIOL (ESTINYL®) TABLETS

Deleted due to low use. Estradiol 0.5 mg, 1 mg, and 2 mg tablets are available.

ETIDRONATE (DIDRONEL®) TABLETS

Deleted due to low use. Alendronate and risedronate are available.

FENOFIBRATE 54 mg AND 160 mg TABLETS

Discontinued by the manufacturer; replaced with 48 mg and 145 mg tablets.

FLUCINONIDE EMOLLIENT (LIDEX-E®) 0.05% CREAM

Deleted due to low use. Fluocinonide 0.05% Non-Emollient (Lidex®) Cream is available.

FOLLITROPIN (FOLLISTIM®) INJECTION

Discontinued by the manufacturer.

KETOCONAZOLE TABLETS

Deleted due to low use. Fluconazole is available.

LEFLUNOMIDE (ARAVA®) 100 mg TABLETS

Deleted due to low use. Leflunomide 10 mg and 20 mg tablets are available.

MEXILETINE (MEXITIL®) 250 mg CAPSULES

Deleted due to low use. Mexiletine 150 mg and 200 mg capsules are available.

DRUGS DELETED FROM STOCK (CON'T)

NORFLOXACIN TABLETS

Deleted due to low use. Ciprofloxacin tablets are available.

PAPAIN AND UREA TOPICAL (ACCUZYME®) OINTMENT

Replaced with Accuzyme® spray.

PENTASTARCH INJECTION

Deleted due to low use.

PHENTERMINE (IONAMIN®) 15 mg CAPSULES

Deleted due to low use. Phentermine 30 mg capsules are available.

PORK REGULAR U-100 INSULIN

Deleted due to low use. Human Regular U-100 insulin is available.

POVIDONE-IODINE 0.3% VAGINAL SOLUTION

Discontinued due to low use.

PROCAINAMIDE 250 mg CAPSULES

Deleted due to low use. Procainamide 500 mg and 750 mg extended-release capsules are available.

SECOBARBITAL CAPSULES

Deleted due to low use. Zolpidem and zaleplon are available.

SODIUM PHENYLBUTYRATE TABLETS AND ORAL POWDER

Deleted due to low use.

SOLUTAR 1.5% IN AQUAPHILIC OINTMENT (CRUDE COAL TAR OINTMENT)

Deleted due to low use.

SULFADOXINE 500 mg WITH PYRIMETHAMINE 25 mg TABLETS

Deleted due to low use. Other antimalarial agents are available.

TETANUS TOXOID INJECTION

Discontinued by the manufacturer. Tetanus toxoid, adsorbed is available.

TETRACAINE (PONTOCAINE®) 20 mg POWDER FOR INJECTION

Deleted due to low use. Tetracaine 10 mg/ml, 2 ml amp is available.

THEOPHYLLINE IMMEDIATE-RELEASE TABLETS

Discontinued by the manufacturer. Theophylline oral liquid is available.

TOCAINIDE TABLETS

Deleted due to low use. Mexiletine capsules are available.

TRIPLE DYE TOPICAL SOLUTION

Deleted due to low use. Other topical anti-infectives are available.

UROKINASE INJECTION

Discontinued by the manufacturer.

ZALCITABINE TABLETS

Deleted due to low use.

ADDITIONAL ACTIONS

ABACAVIR WITH LAMIVUDINE (EPZICOM®) TABLET

A 600 mg abacavir with 300 mg lamivudine tablet has been added to stock.

DIVALPROEX EXTENDED-RELEASE TABLETS

A 250 mg strength was added to stock.

PHARMACY AND THERAPEUTICS SUBCOMMITTEE ACTIONS

ADDITIONAL ACTIONS (CON'T)

ETANERCEPT INJECTION

A 50 mg/1 ml syringe was added to stock.

EZETIMIBE WITH SIMVASTATIN

This combination product (Vytorin®) was added to stock.

FENOFIBRATE (TRICOR®) TABLETS

The 54 and 160 mg fenofibrate tablets have been discontinued by the manufacturer and replaced with 48 and 145 mg tablets. The new tablets can be taken without regard to meals.

HYALURONIDASE INJECTION

A 150 units/1 ml vial has been reintroduced onto the U.S. market.

LEVOFLOXACIN

A 25 mg/ml oral solution was added to stock.

MENINGOCOCCAL CONJUGATE VACCINE TETRAVALENT VACCINE (MENACTRA®) INJECTION

This preparation is indicated in all cases where ACIP recommends meningococcal vaccine for persons 11 through 55 years of age because of the increased immunogenicity. Children 2 through 10 years old and adults over 55 years of age should receive the meningococcal polysaccharide vaccine (Menomune®). Both vaccines cover the same strains (serogroups A, C, Y, and W-135) but have different routes of administration. Menactra® is administered intramuscularly and Menomune® is administered subcutaneously. **The brand name should now be clarified on all orders for meningococcal vaccine.**

MYCOPHENOLIC ACID (MYFORTIC®) DELAYED-RELEASE TABLETS

180 mg and 360 mg strengths were added to stock.

SODIUM TETRADECYL SULFATE INJECTION

A 10 mg/ml, 2 ml vial has been added to stock.

VORICONAZOLE

A 40 mg/ml oral solution was added to stock.

NEW PSEUDOEPHEDRINE CONTROLS TO GO INTO EFFECT ACROSS IOWA

The state of Iowa has enacted a new law affecting the handling of pseudoephedrine products. As of Saturday, May 21, 2005, most pseudoephedrine-containing products sold in Iowa will be handled as Schedule V controlled substances. This new law affects pseudoephedrine provided as a single-agent product and any combination product that contains any amount of pseudoephedrine (including many cough and cold preparations). As with other controlled substances, these products must be stored within pharmacy and all patient care areas under lock and key, and a perpetual inventory of supplies kept on hand must be maintained. Outpatient prescriptions for any pseudoephedrine-containing products will also be treated like other controlled substances in Schedules III, IV and V; the prescriber must supply his/her DEA registration number on the prescription and the number of refills will be limited to five (or six months).

Over-the-counter (OTC) pseudoephedrine-containing products will still be available for purchase in the UIHC Ambulatory Care Pharmacies. However, the new law limits the amount that can be purchased without a prescription to 7500 mg (total) within a 30-day period. Purchasers must be 18 years of age and provide a government-issued photo ID (e.g., a driver's license).

For several years, the UIHC has internally handled single-agent pseudoephedrine products as controlled substances; the new law now requires that all pseudoephedrine-containing preparations be treated as controlled substances throughout Iowa.

Additional information may also be found at:

http://www.state.ia.us/odcp/information_trends/pseudo%20what%20you%20need%20to%20know.html.



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