NEW DRUGS

Generic Drugs

Lamisil for Fungal Nail Infections

The U.S. Food and Drug Administration (FDA) has approved the first generic versions of prescription terbinafine HCl (Lamisil, Novartis) tablets for fungal infections of the nails (onychomycosis).

The FDA approved the tablets in 250-mg formulations for multiple generic drug manufacturers. An application for a generic version of over-the-counter terbinafine HCl 1%, cream (Taro) to treat athlete’s foot has also been approved.

(Source: FDA, July 3, 2007.)

Generic Norvasc for Hypertension

Final approval has been granted to Lupin for its abbreviated New Drug Application (NDA) for amlodipine besylate tablets, 2.5 mg (base), 5 mg (base), and 10 mg (base). Amlodipine is a long-acting calcium-channel blocker indicated for the treatment of hypertension. The tablets are the AB-rated generic equivalent of Pfizer’s Norvasc tablets.

(Source: Lupin, July 17, 2007.)

NEW FORMULATIONS

Rivastigmine (Exelon) Patch

For Alzheimer’s Disease

Novartis has received the FDA’s approval for its rivastigmine tartrate (Exelon) skin patch for patients with mild-to-moderate Alzheimer’s disease. The company said that the patch was designed with compliance in mind and was preferred to capsules by more than 70% of doctors and nurses as a method of drug delivery. The patch is also considered to be helpful in reducing gastrointestinal side effects.

The patch is approved for patients with mild-to-moderate dementia associated with Parkinson’s disease. Exelon capsules are already approved to treat mild-to-moderate Alzheimer’s disease and mild-to-moderate dementia associated with Parkinson’s disease.

Applied once daily to the back, chest, or upper arm, the patch maintains steady blood levels of the drug throughout the day. At higher-than-recommended doses, the patch was associated with nausea, vomiting, diarrhea, appetite loss, and weight loss.

(Source: The Wall Street Journal, July 10, 2007; WebMD, July 9, 2007; FDA.)

Ketoconazole Foam (Extina) For Seborrheic Dermatitis

On June 12, the FDA approved the NDA for ketoconazole foam 2% (Extina, Stiefel Laboratories). This topical agent is indicated for immunocompetent patients 12 years of age and older with seborrheic dermatitis.

Other therapies for this skin condition contain ketoconazole 2% in a cream, gel, or shampoo vehicle. Sold by prescription, the foam is quickly absorbed into the skin.

The foam is applied to the affected skin areas twice a day for four weeks and can be used on hair-bearing and non–hair-bearing skin.

(Sources: Stiefel Laboratories, July 17, 2007; www.extina.com.)

Lower-Dose Oseltamivir (Tamiflu)

The FDA has approved a supplemental NDA (sNDA) for oseltamivir phosphate (Tamiflu, Roche) capsules in strengths of 30 mg and 45 mg. The lower-dose capsules provide a convenient alternative for treating and preventing influenza types A and B in patients one year of age and older. Because the capsules have a longer shelf life (five years) than the liquid suspension formulation (two years), they also offer an improved option for government stockpiling to prepare for a pandemic.

Tamiflu will continue to be available in a 75-mg capsule for adults and in a liquid suspension for children. The 30-mg and 45-mg capsules will be available in pharmacies nationwide and for stockpiling for the 2007–2008 flu season.

To date, Roche has filled orders from the federal government and states for 43.7 million Tamiflu treatment courses. The sNDA was filed in March 2007 based on data available for the 75-mg capsule.

Tamiflu is the only neuraminidase inhibitor approved for use in children one to five years of age. Co-developed by Gilead, it is indicated for the treatment of uncomplicated influenza caused by virus types A and B in patients over one year old who have had flu symptoms for no more than two days.

Tamiflu is also indicated for the prevention of influenza in patients ages one and older.

This medication is not a substitute for annual early vaccination.

(Source: Roche, July 2, 2007.)

NEW INDICATION

Mifepristone (Corlux) For Cushing’s Syndrome

Mifepristone (Corlux, Corcept Therapeutics) has received an orphan drug designation from the FDA for the treatment of Cushing’s syndrome. This disorder is caused by prolonged exposure of the body’s tissues to high levels of the hormone cortisol.

Mifepristone (RU-486) is also used as an abortifacient in the first two months of pregnancy and in smaller doses as an emergency contraceptive.

Corcept is expected to file an investigational NDA shortly.

Corlux has been somewhat effective in ameliorating psychosis and depression in patients with Cushing’s disease. The drug worked quickly, bringing about improvement within seven days after treatment began, and produced minimal side effects.

(Source: Corcept, July 9, 2007.)
**NEW DRUGS**

**LABEL CHANGES**

**Omalizumab (Xolair) For Asthma**

Omalizumab (Xolair, Genentech) injection is approved to treat moderate-to-severe persistent asthma in adults and adolescents 12 years of age and older who have a positive skin test or reactivity in vitro to a perennial aeroallergen and who have not responded adequately to inhaled corticosteroids.

The FDA mandated the revised label because some patients receiving Xolair can experience anaphylaxis. This life-threatening reaction can occur at any dose and up to 24 hours later—even if the patient had no reaction to the first dose. A boxed warning, as well as updated warnings, precautions, and adverse reactions, have been added. A medication guide about the risk of anaphylaxis must be distributed to patients with each dose of omalizumab.

(Sources: FDA, July 5, 2007; www.healthcentral.com/asthma/c/46/11007/xolair-prompts-lesson.)

**Carticel for Cartilage Repair**

The FDA has approved new labeling for autologous cultured chondrocytes (Carticel, Genzyme). The label incorporates data from the Study of the Treatment of Articular Repair (STAR), which investigated patients who responded inadequately to a previous cartilage repair procedure of the knee.

Approved in 1995, Carticel is used by orthopedic surgeons to treat articular cartilage lesions on the thighbone part of the knee caused by trauma that have not responded to previous repair surgery. Carticel was the first cell therapy to be approved by the FDA.

(Source: Genzyme, June 25, 2007.)

**Methadone Warning**

Managed-care pharmacy benefit programs and many state Medicaid pharmacy formularies are choosing to promote the prescribing of methadone as an opioid of choice because of the drug’s low acquisition cost for managing pain. Some programs advise the analgesic use of methadone in place of long-acting and long-term opioids. However, neither the drug’s effectiveness nor efficacy has been exposed to rigorous, double-blind, placebo-controlled trials—and many prescribers remain unaware of an important labeling change introduced last fall.

Methadone has been used for decades for managing substance abuse disorders in patients with a chemical dependency or addiction to opioids. It is indicated for the treatment of moderate-to-severe pain, detoxification therapy for opioid addiction, and maintenance treatment of opioid addiction, in conjunction with social and medical services.

Clinical concerns have arisen because of the association of methadone with prolongation or dispersion of the corrected QT (QTc) interval. When the drug is prescribed without careful monitoring, it has the potential to contribute to morbidity and/or mortality. Several reports describe adverse outcomes in patients who have exceeded the normal therapeutic dose range; who have used other pharmacotherapeutic agents with QTc-prolonging effects; or who have pharmacokinetic, pharmacodynamic, or pathophysiologic comorbidities.

Patients with risk factors for QTc prolongation would benefit from a cardiac evaluation or at least a baseline electrocardiogram before methadone therapy begins.

In November 2006, the FDA notified health care professionals of reports of death and life-threatening adverse events, such as respiratory depression and cardiac arrhythmias in patients receiving methadone.

The warning noted that the elimination half-life of methadone (from 8 to 59 hours) is considerably longer than its analgesic action (four to eight hours). The FDA recommended that the dose of methadone for pain be carefully selected and slowly titrated to anaggesic effect, even in patients who are opioid-tolerant. Physicians should closely monitor patients when switching them from other opioids and when changing their methadone dose; they should also carefully instruct patients on how to take this medication.

The most feared cardiac consequence of methadone is sudden cardiac death resulting from torsade de pointes that degenerates into ventricular fibrillation. Other cardiac adverse events associated with methadone include syncope, hypotension, and ventricular ectopy.

The new boxed warning in the prescribing information is stated as follows:

“Cardiac conduction effects: Laboratory studies, both in vivo and in vitro, have demonstrated that methadone inhibits cardiac potassium channels and prolongs the QT interval. Cases of QT interval prolongation and serious arrhythmia (torsades de pointes) have been observed during treatment with methadone. These cases appear to be more commonly associated with, but not limited to, higher-dose treatment (greater than 200 mg/day). Most cases involve patients being treated for pain with large, multiple daily doses of methadone, although cases have been reported in patients receiving doses commonly used for maintenance treatment of opioid addiction.”

Patients should avoid consuming grapefruit juice concurrently because it decreases the clearance of the methadone enantiomers.


continued on page 425
Ezetimibe and simvastatin together were more effective in lowering low-density lipoprotein-cholesterol (LDL-C) and C-reactive protein (CRP) levels, compared with either drug as monotherapy, say researchers from University of Rochester, New York, and Methodist DeBakey Heart Center and Baylor College of Medicine in Houston, Texas.

In three identical prospective trials, patients were randomly assigned to receive placebo; ezetimibe (e.g., Zetia) 10 mg; ezetimibe 10 mg added to simvastatin (e.g., Zocor) 10, 20, 40, or 80 mg; or simvastatin 10, 20, 40, or 80 mg.

After 12 weeks of treatment, when averaged across the doses, the ezetimibe/simvastatin combination (e.g., Vytorin) produced significantly greater reductions from baseline in LDL-C levels, compared with simvastatin alone (53% vs. 38%). At each dose tested, the combination treatment was significantly more effective at lowering LDL-C, compared with each milligram-equivalent dose of simvastatin monotherapy.

Median baseline CRP values were similar for all individual treatment groups. Again, when averaged for all doses, ezetimibe/simvastatin showed significantly greater reductions in CRP compared with monotherapy. Ezetimibe/simvastatin and atorvastatin were similar in lowering CRP from baseline levels (25.1% vs. 24.8%).

The combination’s enhanced effect on CRP was consistent for each patient subgroup, regardless of age, sex, race, body mass index, diabetes, coronary heart disease, and metabolic syndrome. The greatest reduction in CRP levels occurred in patients with the highest CRP levels in the baseline evaluation.

Zocor is manufactured by Merck. Zetia and Vytorin are manufactured by Merck in partnership with Schering-Plough.

(Source: *Am J Cardiol* 2007;99:1706–1713.)

**Heart Disease, Bleeding, and SSRIs**

Patients with acute coronary syndrome (ACS) who receive selective serotonin reuptake inhibitors (SSRIs) are more likely to have bleeding episodes but less likely to have recurrent myocardial ischemia and heart failure, according to a Johns Hopkins study. The researchers say this is the first study to examine the association.

In the study, 1,254 patients were admitted with ACS and received a glycoprotein IIb/IIIa inhibitor. Approximately one in seven patients had a history of depression; 158 were treated with an SSRI during their hospital stay. Nearly half were given
sertraline, followed by fluoxetine (Prozac, Eli Lilly), paroxetine (Paxil, GlaxoSmithKline), escitalopram (Lexapro, Forest), and citalopram (Celexa, Forest). Almost all matched patients received aspirin (99%), clopidogrel (Plavix, BMS/Sanofi) (95%), and heparin (98%).

Ninety-eight patients experienced major bleeding; 287 had minor bleeding, and 34 had gastrointestinal bleeding. Although patients who received an SSRI were significantly more likely to experience any bleeding (37%), compared with patients not taking SSRIs (27%), the difference was principally a result of an increase in the risk of minor bleeding.

Patients who were not taking SSRIs had twice the risk (14%) of a minor adverse event (e.g., recurrent myocardial ischemia, heart failure, or asymptomatic cardiac enzyme elevation), compared with those not receiving SSRIs (7%).


Name: C-QURLite Mesh
Manufacturer: Atrium Medical Corp., Hudson, NH
Approval Date: April 19, 2007
Use Classification: C-QURLite Mesh is indicated for use in the repair and reinforcement of soft tissue, including hernia repair and laparoscopic and open surgical procedures.

Description: The advanced lightweight surgical mesh is constructed from refined polypropylene monofilament, providing a strong low-profile, lightweight base structure. The natural omega-3 fatty acid, bioabsorbable gel coating is then applied to each monofilament of the mesh to enhance handling of the material and subsequent healing.

Purpose: This technology combines Atrium’s polypropylene surgical mesh with a pharmaceutical-grade gel coating. This nonpolymeric, bioabsorbable coating has demonstrated improved anatomical conformance by diminishing aggressive, dense acellular collagen formation that often results in adhesions following surgery.

Benefit: Unlike traditional tissue-separating mesh products, C-QURLite Mesh enhances the handling stiffness and healing response in pre-peritoneal placement, compared with “bare” polymer mesh products used in hernia repair. The device helps to minimize peri-}

{continued on page 458}
product is applied topically to help control oozing from small blood vessels during vascular surgery.

**Description:** Derived from pooled human plasma, Evicel consists of a fibrinogen concentrate and thrombin, which promote clotting. Both substances reduce the risk of viral transmission in manufacturing; however, the potential risk for the transmission of blood-borne viruses cannot be totally eliminated.

**Purpose:** Evicel was approved in 2003 as an adjunct to hemostasis in patients undergoing liver surgery when control of bleeding by conventional surgical techniques (suture, ligature, cautery) was ineffective or impractical. It is not indicated in massive or brisk arterial bleeding.

**Benefit:** Evicel is the only commercially available fibrin sealant that is bovine-free and aprotinin-free. It is ready to use in less than one minute after thawing, and it forms a clear, stable clot that anchors firmly to the bleeding site.

**Sources:** www.pharmacyonesource.com; www.jnjgateway.com; FDA News, May 15, 2007

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**Devices in the News**

**Boxed Warning**

The FDA has asked manufacturers to include a boxed warning on the labeling of all gadolinium-based contrast agents that are used to enhance the quality of magnetic resonance imaging (MRI). The warning states that patients with severe kidney insufficiency who receive gadolinium-based agents are at risk for developing a debilitating, potentially fatal disease, nephrogenic systemic fibrosis (NSF).

The labeling would also state that the risk is higher for patients just before or just after they undergo liver transplantation and for patients with chronic liver disease if they are experiencing kidney insufficiency of any severity.

Patients with NSF experience thickening of the skin, connective tissues, and other organs. This sequela inhibits the ability of patients to move and may cause broken bones. The cause of NSF is not known, and no consistently effective therapy is available.

**Source:** www.fda.gov/bbs/topics/NEWS/2007/NEW01638.html

**Cardiac Stent**

Johnson & Johnson’s Cordis unit, which makes cardiovascular devices, has resolved its problems with the FDA, clearing the way for the introduction of new products. Known for its Cypher drug-coated heart stent, Cordis has been operating under a warning from the FDA since April 2004.

Regulators had cited problems with internal procedures, including manufacturing processes. The company can now proceed with introducing the next generation of its Cypher stent, which is considered to be a competitor with Boston Scientific’s Taxus drug-eluting stent.

**Source:** www.therapeuticsdaily.com