NEW DRUGS

NEW DRUG

Deferasirox, Iron Chelator

The U.S. Food and Drug Administration (FDA) has approved a once-daily oral iron chelator, deferasirox (Exjade®, Novartis), for the treatment of chronic iron overload caused by blood transfusions in adults and children two years of age and older.

This is the only iron chelator that is given as a drink. The tablets are dispersed in a glass of water, orange juice, or apple juice. The current standard of care often requires a subcutaneous infusion lasting eight to 12 hours each night for five to seven nights a week as long as the patient is receiving transfusions or has excess iron within the body.

Iron overload is a potentially life-threatening and unavoidable consequence of frequent blood transfusions that are used to treat certain types of rare, chronic blood disorders, such as thalassemia, sickle cell disease, rare anemias, and myelodysplastic syndromes.

This approval is expected to enhance the acceptance of iron chelation therapy, especially for children, and it offers a new alternative to the burdensome continuous infusion therapy.

(Source: Novartis, November 2, 2005.)

NEW INDICATIONS

Nelarabine for Leukemia And Lymphoma

GlaxoSmithKline has announced the accelerated approval of nelarabine (Arranon®) Injection by the FDA. This chemotherapy agent is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to, or has relapsed following treatment with, at least two chemotherapy regimens.

This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefits have not been conducted. Postmarketing evaluation will be pursued though a randomized, multi-center phase 3 trial.

In December 2003, nelarabine received a “fast track” designation and was later granted orphan drug status. In September 2005, the FDA’s advisory committee voted to recommend that the FDA grant accelerated approval of nelarabine for both children and adults.

(Source: GlaxoSmithKline, October 28, 2005.)

Atorvastatin May Reduce Risk of Stroke, Heart Attack in Diabetes

Pfizer Inc. has announced the FDA’s newest indication for atorvastatin calcium (Lipitor®): to reduce the risk of stroke and heart attack in people with type-2 diabetes and to reduce the risk of stroke in people without diabetes but with other risk factors.

The FDA’s decision was based on the findings of the Collaborative Atorvastatin Diabetes Study (CARDs). This landmark trial involved more than 2,800 patients with type-2 diabetes, near-normal cholesterol levels, and at least one other risk factor (e.g., high blood pressure or smoking). The results showed patients taking atorvastatin experienced nearly 50% fewer strokes than those taking placebo.

The trial was stopped two years early because of the strong benefits shown.

This additional indication also reflects findings from The Anglo-Scandinavian Cardiac Outcomes Trial: Lipid-Lowering Arm (ASCOT–LLA). In this trial, atorvastatin also reduced the relative risk of stroke by 26% compared with placebo.

According to the American Diabetes Association’s recommended treatment guidelines, adults with type-2 diabetes should be considered for statin therapy regardless of their low-density lipoprotein-cholesterol levels.

(Source: Pfizer Inc., September 27, 2005.)

Adalimumab for Psoriatic Arthritis

The FDA has approved adalimumab (Humira®, Abbott) for reducing signs and symptoms of active arthritis in patients with psoriatic arthritis (PsA).

PsA is a chronic autoimmune disease that combines the symptoms of arthritis (joint pain and inflammation) with those of psoriatic skin disease (dry, scaly skin). It is the first new disease indication for this agent since its approval for rheumatoid arthritis (RA).

This approval is based on results of the Adalimumab Effectiveness in Psoriatic Arthritis Trial (ADEPT). At 24 weeks, treated patients improved in both joint and skin disease symptoms more than placebo patients did.

The recommended dose for PsA is 40 mg every other week by subcutaneous injection.

Abbott received European approval for PsA and early severe RA on August 8, 2005.

(Source: Abbott Labs, October 4, 2005.)

Exemestane for Early Breast Cancer

Pfizer Inc. has received the FDA’s approval to market exemestane tablets (Aromasin®) for the adjuvant treatment of postmenopausal women with estrogen receptor–positive early breast cancer after two to three years of tamoxifen therapy. Adjuvant therapy is given following surgical removal of a primary tumor.

This drug was approved in the U.S. in 1999 for the treatment of advanced breast cancer in postmenopausal women whose tumors had stopped responding to tamoxifen.

For more information on this topic, please see the Pharmaceutical Approval Update article on page 676.

(Source: Pfizer Inc., October 5, 2005.)
New Warning for Duloxetine

Eli Lilly and the FDA have notified health care professionals of a revision to the precautions/hepatotoxicity section of the prescribing information for duloxetine HCl (Cymbalta®). This medication is indicated for the treatment of major depressive disorder and diabetic peripheral neuropathic pain.

Postmarketing reports of hepatic injury, hepatitis, and cholestatic jaundice suggest that patients with pre-existing liver disease who take duloxetine may have an increased risk for further liver damage. The new labeling extends the precaution against using this drug in patients with substantial alcohol use to include patients with chronic liver disease.

Duloxetine should not be given to patients with hepatic insufficiency.

(Source: FDA, October 19, 2005.)

Long-Term Benefits of ACE-Inhibitors, Angiotensin-Receptor Blockers

Findings from a meta-analysis of 66,608 patients in 11 trials are clear: blocking the renin–angiotensin system with an angiotensin-converting enzyme (ACE)–inhibitor or an angiotensin-receptor blocker (ARB) significantly reduces the odds of developing type-2 (non–insulin-dependent) diabetes. However, researchers from the University of Connecticut say that the beneficial results occur regardless of whether ACE-inhibitors or ARBs are used.

Although there may be pharmacological differences between the drugs, they do not seem to matter in terms of a person’s risk of developing diabetes. Although the 11 studies did not show an effect on cardiovascular, cerebrovascular, or mortality outcomes in the short term, the long-term benefits of these medications in preventing diabetes appear possible.

(Source: Chest 2005;128:496–506.)

Inappropriate Prescribing in Elderly Veterans

“Despite many previous studies, we are only beginning to understand the phenomenon of inappropriate prescribing,” say researchers who used a retrospective national Veterans Administration database analysis.

They found that about one third of elderly veterans may have been exposed to potentially inappropriate drugs. The availability of a comprehensive national data source, the investigators say, allowed a closer examination of a problem that has been often discussed but not yet solved.

The study relied on a list of 11 drugs that should always be avoided, eight drugs that are indicated on rare occasions, and 14 drugs that have some indications but that are often misused. An expert panel at the Agency for Healthcare Research and Quality (AHRQ) developed the list.

The bulk of inappropriately prescribed drugs consisted of pain relievers, benzodiazepines, antidepressants, and musculoskeletal agents. Caucasian patients, patients with psychiatric comorbidities, and patients taking more than one prescribed drug were the ones most likely to receive inappropriate drugs.


Clot-Dissolving Drugs May Help Even Mild Stroke Symptoms

Although use of the clot-dissolving drug called tissue plasminogen activator (tPA) has revolutionized the treatment of patients with acute stroke, many patients are not receiving the drug because their initial symptoms appear mild or may improve soon after they arrive at the hospital. A study from Massachusetts General Hospital has confirmed that eligible patients who do not receive tPA face a significant risk of disability.

About 30% of patients who were judged as “too good to treat” either died or were discharged to a rehabilitation facility. The researchers were not able to find features that could predict which of the untreated patients would have problems.

tPA can safely dissolve a clot when a stroke is caused by a blocked blood vessel if it is given within three hours of symptom onset. Sometimes it can completely reverse the effects of the stroke.

Many patients do not arrive at a hospital soon enough to receive the drug, but even when they do, physicians must weigh the small but significant risk that tPA may cause hemorrhaging in the brain. Because of this risk, patients with less severe symptoms may not receive tPA, and it is hoped that they will recover
NEW DRUGS

DRUG NEWS

continued from page 625

on their own. An earlier study had suggested that many of those patients would not do well and led to the current investigation.

The lead author of the study explains that rapid symptom improvement early in the course of a stroke may reflect the affected area of the brain as it “borrows” blood from nearby areas; however, if the initial blockage affects the primary blood supply and is not removed, symptoms may eventually worsen. The author recommends that physicians be cautious if they decide not to use tPA and that they also evaluate the patient’s gait.

(Sources: Massachusetts General Hospital, October 6, 2005; Stroke online, November 2005.)

Experimental Vaccine Helps Prevent Cervical Cancer

The first large study of a vaccine called Gardasil (Merck) showed that it prevented 100% of cervical pre-cancers and noninvasive cervical cancers caused by the human papillomavirus (HPV). Merck plans to seek the FDA’s approval for the vaccine before the end of the year.

HPV infection has been identified as the cause of cervical cancer, pre-cancers, benign cervical lesions, and genital warts. Cervical cancer causes about 290,000 deaths worldwide each year.

It is estimated that 20 million men and women in the U.S. are infected with HPV. Usually, there are no symptoms, and the infection clears up by itself. However, the virus can lead to cervical cancer in some women. It is also associated with abnormal Pap test results.

The findings were reported in October at a meeting of the Infectious Disease Society of America in San Francisco.

In the study, none of the women who received the vaccine went on to develop either pre-cancer or invasive cervical cancer associated with HPV types 16 and 18, which are thought to cause 70% of cervical cancers. HPV types 6 and 11 are associated with 90% of genital warts.

Over two years of follow-up, the vaccine reduced the risk of cervical cancer by 97%. There was one case of cervical cancer in the vaccinated group but 36 cases among women who received placebo.

The results are impressive, but more data are needed before the vaccine can be given to the public. Merck is testing the vaccine in girls and boys as young as nine years of age, and the FDA will decide whether the product should be sold for use in preteens.

(Sources: Health Day News, Scout News; USA Today, October 6, 2005 New York University School of Medicine, American Cancer Society.)
Diabetes Drug Muraglitazar: More Studies Needed

Researchers at the Cleveland Clinic warn that the use of an investigational diabetes drug called muraglitazar (Pargluva, Bristol-Myers Squibb/Merck) may double the risk of death, heart attack, and stroke. They say that the FDA should not approve the drug until its cardiovascular safety can be proven in a “dedicated” trial of cardiovascular events. The FDA had issued an approvable letter.

The drug is a dual alpha/gamma peroxisome proliferator-activated receptor (PPAR) activator. It targets both glycated hemoglobin (HbA1c) and serum lipids.

(Sources: JAMA, MedPage Today, October 20, 2005.)

Trastuzumab Lowers Breast Cancer Recurrence

The targeted drug trastuzumab (Herceptin®, Roche/Genentech), previously shown to prolong survival in advanced breast cancer, may dramatically reduce the rate of recurrence in patients with early-stage disease when given for one year following standard chemotherapy.

These are encouraging findings in an interim report from the Herceptin Adjuvant (HERA) trial, which includes more than 5,000 patients in 39 countries.

Women whose tumors were HER2-positive (overexpressing a protein associated with more aggressive cancer and poorer outcomes) had a 50% lower risk of disease recurrence, or an 8% improvement in the number of women who were free of disease two years after beginning the treatment.

Herceptin® is a monoclonal antibody–based drug that blocks the activity of the HER2 protein, a growth factor receptor that is overexpressed in cancer cells of 20% to 30% of breast cancer patients. HER2-positive tumors, which can be identified when the breast cancer diagnosis is made, are generally more prone to spreading and are resistant to many chemotherapy agents.

Recurrences in HER2-positive breast cancer tend to happen in the first year or two. When the statisticians examined the data after one year, the benefits in the Herceptin® group were already apparent. Women receiving the drug had a significant improvement in disease-free survival of 8.4% at two years. The study is planned to run through 2008.

The researchers were gratified to discover that only 0.5% of patients receiving Herceptin® had serious cardiac adverse effects. The scientists suggested that the lower incidence of cardiac effects in the HERA Trial might be related to the facts that Herceptin® was administered after chemotherapy treatment instead of simultaneously and that patients with insufficient cardiac function after chemotherapy were not included.

(Sources: N Engl J Med, October 5, 2005; Dana-Farber Cancer Institute; www.sciencedaily.com.)

Genes and Schizophrenia Risk

A study has found that a genetic defect in some people can trigger a dangerous increase in levels of dopamine, a critical neurotransmitter in the brain. It is thought that these elevated levels may lead to schizophrenia.

Although the cause of this mental illness is not clear, there is evidence for a biological or genetic basis.

The study investigated 24 adolescents with a genetic mutation, or deletion, to part of chromosome 22. The deletion occurs in one in 4,000 births. Children with the deletion have higher than normal levels of dopamine.

After observing the adolescents for five years, the scientists found that about one-third developed schizophrenia in that time. Even though the deletion probably caused fewer than 5% of cases, it is the only well-defined genetic risk factor that is known at this time.

(Source: Nature Neurosci (online), October 23, 2005; The Independent (online), October 24, 2005.)

Paroxetine: Linked To Birth Defects?

The FDA and GlaxoSmithKline have alerted physicians about a new study on birth defects in babies born to women who took the antidepressant paroxetine (Paxil®) during the first trimester of pregnancy. In a study of more than 3,500 pregnant women, paroxetine was linked to twice as many major birth defects as other antidepressants, according to the FDA.

Birth defects are rare in the U.S., and it is not certain what role, if any, the drug might have played, notes GlaxoSmithKline. Most of the defects were related to the heart. In this retrospective epidemiological study, there were no data on birth defects in babies born to women who did not take antidepressants during early pregnancy.

Some studies of paroxetine during pregnancy have suggested an increased risk of fetal malformations, but others have not.

Antidepressants have been linked to withdrawal symptoms in babies born to mothers taking selective serotonin reuptake inhibitors (SSRIs).

Health care professionals are being advised to weigh the potential risks and benefits of using this drug in pregnant women and to discuss these findings as well as treatment alternatives with their patients. Patients should tell their doctors if they are pregnant, plan to become pregnant, or are breast-feeding.

GlaxoSmithKline will include the results of the study in the list of precautions on the drug’s product labeling.

(Sources: FDA, September 27, 2005; GlaxoSmithKline; © 2005 WebMD Inc.)
NEW DRUGS

Tentative Approval: Ribasphere® for Hep C

Three Rivers Pharmaceuticals, LLC has announced that the FDA has granted tentative approval for its ribavirin (Ribasphere®) tablets in dosage strengths of 200 mg, 400 mg, and 600 mg in combination with interferon alfa-2a for the treatment of chronic hepatitis C (HCV).

Ribavirin is a synthetic nucleoside analogue with antiviral activity. It is marketed by Roche under the brand name Copegus®. Final approval is expected upon the expiration of the brand exclusivity in December 2005. The products will be co-marketed by Three Rivers and its marketing partner PAR.

(Source: Three Rivers, October 24, 2005.)

NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: Total Temporomandibular Joint Replacement System
Manufacturer: Walter Lorenz Surgical, Inc., Jacksonville, FL
Approval Date: September 21, 2005
Use Classification: The system is indicated for patients needing a total jaw replacement because of severe arthritis, fused joints, previous multiple surgeries, fractures, tumors, degenerated joints, or developmental abnormalities that cannot be treated by other means.

Description: This is a ball-and-socket joint with one side mounted to the jaw and the other side mounted to the head in front of the ear. A surgeon implants the joint after removing any old devices, unsuccessful grafts, and damaged bone.

Purpose: The device may reduce jaw pain, decrease interference with eating, and increase the patient’s ability to open the mouth. Patients who have had many previous jaw surgeries may have more complications during joint reconstruction.

Benefit: The goal of total jaw replacement is to relieve the pain in the joint caused by damaged cartilage. The pain may be so severe that a person may avoid using the joint to its fullest extent, weakening the muscles around the joint and making it even more difficult to move the joint.

Source: www.fda.gov/cdrh/mda/docs/p020016.html

Name: Orbasone Pain Relief System
Manufacturer: Orthometrix, Inc., White Plains, NY
Approval Date: August 10, 2005
Use Classification: The system uses strong sound waves (extracorporeal shock wave energy) to relieve proximal plantar fasciitis (heel pain).

Description: This electrohydraulic device uses the spark-gap method to create a shock wave. An electrode (spark plug) ignites an electrical charge within a water-contained, stainless steel, semi-ellipsoid chamber and contact membrane. This action causes evaporation of a small portion of the water and creates a shock wave that reflects outward off the ellipsoid. The shock wave is generated within the reflector chamber and is transmitted through the skin surface to the treatment site. Coupling solution is used on both the contact membrane and the patient’s skin during treatment to enhance conductivity.

Purpose: The system is designed to relieve inflammation of the plantar fascia, the connective tissue that stretches from the base of the toes, across the arch of the foot, and inserts into the heel bone. Proximal plantar fasciitis is heel pain in the area where the plantar fascia inserts into the heel bone. The device is used to treat heel pain with or without heel spurs in patients 18 years of age or older.

Benefit: The system provides a non-invasive alternative to surgery.

Precautions: Potential adverse events include bruising, mild edema, pain, swelling, and tingling.

Source: www.fda.gov/cdrh/mda/docs/p040039.html

Name: Wingspan™ Stent System with Gateway™ Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter
Manufacturer: Boston Scientific/Smart Therapeutics, San Leandro, CA
Approval Date: August 3, 2005
Use Classification: The catheter is used to open blocked arteries in the brain, allowing blood to flow to the brain.

Description: A balloon catheter is inserted through the blood vessels, across the blockage. It is then inflated to open the blockage. A preloaded delivery system is inserted through the same path as the balloon catheter and carries the stent to the blockage site. A stent is deployed across the blockage. The stent is a self-expanding, metal (nitinol) mesh in the shape of a tube. As the stent is positioned, it expands to conform to the inside contour of the artery wall. The delivery system is then withdrawn. The expanded stent holds the blocked artery open.

Purpose: The Wingspan™ System is designed to open blockages in arteries of the brain before the stent is inserted.

Benefit: The catheter is used to open blocked arteries in the brain when clot-dissolving drugs have not worked. The stent provides a barrier to reduce the risk of recurrent blockage or narrowing of the artery and to support the artery wall.

Precautions: The system should not be used in patients who cannot take anti-platelet or anticoagulation drugs to help prevent blood clots or who have a lesion that is highly calcified or that might prevent access, balloon angioplasty, or appropriate expansion of the stent.

Source: www.fda.gov/cdrh/mda/docs/h050001.html

continued on page 669
Recalled Devices

**VeriCal® Calibrator Set.** On October 6, 2005, BioMerieux and the FDA notified health care professionals of a recall of the VeriCal® Calibrator Set. The set calibrates prothrombin times and activated partial thromboplastin times on the company’s instrument platforms. This recall affects only International Normalized Ratio determinations derived from prothrombin times on the Multichannel Discrete Analyzer® (MDA) Coag-a-Mate MTX and MAX platforms.

The product is being recalled because of the faulty assignment of International Sensitivity Index (ISI) values associated with the set. These calibrated ISI values are currently provided on Simplastin® HTF (human tissue factor) and Simplastin® L product labeling. The labeling contains PT in seconds, but is being revised to include ISI assignment for specified reagents.

**Source:** [www.fda.gov/medwatch/safety/2005/safety05.htm#VeriCal](http://www.fda.gov/medwatch/safety/2005/safety05.htm#VeriCal)

**Enteryx® Liquid Polymer.** The FDA and Boston Scientific have notified health care professionals and patients about adverse events (ADEs), including death, occurring in patients treated with Enteryx®, a liquid chemical polymer that is injected into the lower esophageal sphincter to treat gastro-esophageal reflux disease (GERD). On September 23, 2005, Boston Scientific issued a recall of all Enteryx® Procedure Kits and Injector Single Packs.

Physicians should stop injecting Enteryx® immediately and should follow the manufacturer’s procedures for returning the unused product. The FDA also provided recommendations for avoiding future ADEs.

**Source:** [www.fda.gov/medwatch/safety/2005/safety05.htm#Enteryx](http://www.fda.gov/medwatch/safety/2005/safety05.htm#Enteryx)