NEW DRUGS

Drug Approved to Treat Cyanide Poisoning

The U.S. Food and Drug Administration (FDA) has approved Cyanokit for the treatment of known or suspected cyanide poisoning. The approval was based on evidence of the drug’s effectiveness in animals.

Cyanokit contains hydroxocobalamin, intravenous (IV) tubing, and a sterile spike for reconstituting the product with saline.

Cyanokit received a priority review and was approved under the Animal Efficacy Rule, which allows the use of animal data for evidence of a drug’s effectiveness for certain conditions when the drug cannot be ethically or feasibly tested in humans.

In a controlled study in cyanide-poisoned adult dogs, the use of Cyanokit reduced whole blood cyanide concentrations by approximately 55% by the end of the infusion, and significantly improved survival of the treated dogs, compared with dogs receiving placebo.

The safety, metabolism, and excretion of Cyanokit were evaluated in 136 healthy adults. At the proposed starting dose of 5 g, the drug was generally well tolerated, with mild-to-moderate side effects.

The drug exits the body unchanged in the urine. In the presence of cyanide, the active drug takes up the cyanide and becomes a form of vitamin B_{12}.

Cyanokit is manufactured by EMD Pharmaceuticals, Inc., by Merck Sante s.a.s. in France and is packaged by Dey Laboratories in California.


Generic Drug Approvals

Generic Cefzil for Infections

Ranbaxy Pharmaceuticals, Inc., has received approval from the FDA to manufacture and market cefprozil tablets USP, 250 mg and 500 mg. The formulations are bioequivalent to, and have the same therapeutic effect as, Cefzil tablets, made by Bristol-Myers Squibb.

Cefprozil is indicated for patients with mild-to-moderate infections caused by susceptible strains of the designated microorganisms in some conditions, such as pharyngitis, tonsillitis, otitis media, acute sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated skin and skin-structure infections.

(Source: FDA, December 14, 2006.)

Generic Extended-Release Wellbutrin

The FDA has approved the first generic version of Wellbutrin XL (bupropion HCl) extended-release tablets, which are indicated for the treatment of Major Depressive Disorder (MDD). The tablets, available in strengths of 150 mg and 300 mg, are manufactured by Anchen Pharmaceuticals, Inc.

(Source: FDA, December 15, 2006.)

Paliperidone for Schizophrenia

The FDA has approved paliperidone (Invega) extended-release tablets for the treatment of schizophrenia. Paliperidone is a new molecular entity and contains an active substance that has never before been approved for marketing in any form in the U.S. Paliperidone is the principal active metabolite of risperidone, a marketed drug for treating schizophrenia.

Schizophrenia is a chronic, disabling mental disorder that affects more than two million Americans. Symptoms include hallucinations, delusions, disordered thinking, movement disorders, social withdrawal, and cognitive deficits.

The effectiveness of paliperidone in the acute treatment of schizophrenia was established in three six-week, placebo-controlled trials conducted in North America, Europe, and Asia.

The recommended dose range is 3 mg to 12 mg/day.

The drug’s effectiveness has not been studied in placebo-controlled trials for longer than six weeks, and patients who use the drug for extended periods should be periodically re-evaluated by a physician.

Paliperidone is manufactured by Alza Corporation for Janssen.

(Source: FDA, December 20, 2006.)

NEW INDICATIONS

Bortezomib for Aggressive Non-Hodgkin’s Lymphoma

Millennium Pharmaceuticals has received the FDA’s approval of bortezomib (Velcade) for the treatment of patients with mantle-cell lymphoma who have received at least one prior therapy. Mantle-cell lymphoma, an uncommon and aggressive form of non-Hodgkin’s lymphoma, affects about 10,000 patients in the U.S.

Bortezomib is indicated for patients with multiple myeloma who have received one prior therapy. The new approval marks the first indication for this agent in therapy for lymphoma.

The approval was based on data from PINNACLE, a prospective, multicenter, single-arm, open-label trial. Response rates to bortezomib were based on an independent radiological review of computed tomography scans.

(Source: Millennium, December 8, 2006.)

Balsalazide Approved for Ulcerative Colitis In Young Patients

Balsalazide disodium (Colazal, Salix) has been approved for the treatment of mildly to moderately active ulcerative colitis in patients 5 to 17 years of age. The condition is a type of inflammatory bowel disease and affects about 5 out of 100,000 pediatric patients in the U.S. each year.
Balsalazide, for pediatric use, was granted orphan drug status under the FDA’s orphan drug program, which provides financial incentives for firms that develop therapies for diseases affecting fewer than 200,000 patients a year. This medication was previously approved for use in adults with mildly to moderately active ulcerative colitis.

The drug’s safety and effectiveness in children was demonstrated in 68 patients who received either 6.75 g or 2.25 g each day for eight weeks. In this study, 45% of the children receiving the higher dose and 37% getting the lower dose showed clinical improvement in rectal bleeding and in the appearance of the gastrointestinal mucosa.

(Source: FDA, December 20, 2006.)

**Celecoxib Approved for Juvenile Rheumatoid Arthritis**

The FDA has approved celecoxib (Celebrex, Pfizer) for the relief of the signs and symptoms of juvenile rheumatoid arthritis (JRA) in patients two years of age and older.

JRA is an autoimmune disease that affects from 30,000 to 60,000 children in the U.S. It is associated with joint swelling, pain, decreased range of motion and abnormalities of growth and development. In some cases, systemic complications may develop, including uveitis, a chronic inflammation of the eye. In severe, uncontrolled cases, permanent disability may occur because of progressive joint damage.

In a 24-week study that enrolled 242 patients between ages two and 17 years, commonly reported side effects were cough, cold, upper respiratory tract infection, abdominal pain, headache, fever, nausea, diarrhea, and vomiting.

This drug has not been studied in patients younger than two years of age, in those who weigh less than 22 pounds, or in patients with signs of having systemic-onset JRA, a more serious type of JRA associated with high fever and rash.

As a COX-2 selective nonsteroidal anti-inflammatory drug (NSAID), celecoxib was originally approved in 1998 for relieving signs and symptoms of rheumatoid arthritis and osteoarthritis in adults.

(Source: FDA, December 18, 2006.)

**NEW FORMULATIONS**

**Chewable Contraceptive For Women**

A contraceptive called Femcon Fe (Warner Chilcott) now offers women the option of chewing a daily tablet to prevent pregnancy. The drug’s active ingredients and doses provide effective cycle control and may be a good choice for women who are experiencing breakthrough bleeding with their current oral agent.

When taken correctly, oral contraceptives have a failure rate of less than 1% per year. However, 47% of women may miss one or more pills per month.

Femcon Fe contains the same active ingredients found in other combination oral contraceptives: a progestin, norethindrone 0.4 mg, and an estrogen, ethinyl estradiol 35 mcg.

Available in a 28-day regimen, each blister-package contains 21 white tablets with the norethindrone acetate/ethinyl estradiol combination (Femhrt, Warner Chilcott), followed by seven “reminder” brown (inactive) tablets to complete a four-week-cycle. The inactive tablets contain 75 mg of ferrous fumarate (iron).

The tablet may be chewed, followed by a full glass of liquid, or swallowed whole.


**Aripiprazole Injection For Rapid Control of Agitation**

Aripiprazole (Abilify, Bristol-Myers Squibb/Otsuka) is now available as an intramuscular injection. This clear, colorless, sterile, aqueous solution provides rapid control of agitation in adults with schizophrenia or bipolar mania at two hours. The injection was approved on September 20, 2006.

This injectable formulation is the first ready-to-use single-dose vial (9.75 mg/1.3 ml) of an atypical antipsychotic drug to calm agitated patients.

Patients who are acutely agitated require immediate assessment and intervention. Excessive motor or verbal activity, irritability, verbal outbursts or abuse, and threatening behavior or language characterize acute agitation.

According to the prescribing information, the oral form should replace the injection as soon as possible if ongoing aripiprazole therapy is indicated.

Many physicians state that they would prefer to start with an injectable agent in the acute setting and then gradually switch to the oral formulation for long-term management.

Physicians who choose to prescribe aripiprazole for an extended duration should re-evaluate the long-term usefulness of the drug periodically for each patient.

(Source: December 12, 2006.)

**Flu Vaccine: A Risk of Guillain-Barré Syndrome?**

Since 1976, reports have suggested that getting a flu shot increases the risk of Guillain-Barré syndrome (GBS) by as much as eight-fold. Researchers from the University of Toronto and Toronto General Hospital who conducted two studies found a slighter, but still significant, risk; it is 43% higher in the immediate period after vaccination.

In a self-matched case series of 1,601 patients who were hospitalized for GBS, 269 were found to have newly diagnosed GBS within 43 weeks of receiving flu vaccine in October or November. In a time-
series analysis, the researchers identified 2,173 hospital admissions for GBS, equivalent to about 170 new cases per year. However, they found no noticeable increase in the incidence of GBS after a mass public influenza vaccination program was introduced in 2000.

(Source: Arch Intern Med 2006;166:2217–2221.)

**Sunitinib Therapy and Hypothyroidism**

Sunitinib (Sutent, Pfizer), while a blessing for some patients with gastrointestinal stromal tumors (GISTs) that are resistant to imatinib mesylate (Gleevec, Novartis), may come with a downside for others: thyroid toxicity. It has become “increasingly evident,” say researchers who conducted a study of sunitinib at Brigham and Women’s Hospital in Boston, that agents designed to block the activity of specific kinase activities may cause “unexpected complications.” More than half of the patients in their study experienced some level of thyroid dysfunction during sunitinib treatment.

Of 42 patients treated for 10 to 167 weeks, 26 had documented abnormal serum concentrations of thyroid-stimulating hormone (TSH). In seven patients, the elevations were mild and transient; however, four patients experienced TSH suppression, and persistent primary hypothyroidism developed in 15 patients. Thyroid function had been normal in all of these patients before the drug treatment.

The longer the course of treatment, the higher the risk. The 15 patients with hypothyroidism had been receiving sunitinib therapy for an average of 50 weeks.

The researchers suggest measuring TSH frequently, for example, every two to three months. A low serum TSH concentration and mild symptoms suggesting thyroiditis-induced thyrotoxicosis may precede the onset of hypothyroidism.

In six of the 15 patients with hypothyroidism, TSH concentrations were suppressed before hypothyroidism developed, suggesting thyroiditis. The researchers warned that the condition might progress rapidly from mild to profound hypothyroidism.

An abnormal serum TSH value should prompt thorough evaluation. Patients who develop overt hypothyroidism should be treated with levothyroxine (e.g., Synthroid, Abbott), and treatment should be considered even in patients with subclinical disease.

The sunitinib treatment does not need to be stopped to treat hypothyroidism. This is good news, because sunitinib is the only drug shown to improve survival in these patients.


**Interferon: Reduce the Dose, Increase the Frequency?**

A lower dose of interferon (IFN) given twice daily to cancer patients was as effective as an intermediate dose given once a day, and patients considered it better in terms of their quality of life.

In a study involving 118 patients with metastatic renal cell cancer at M.D. Anderson Cancer Center in Houston, 50% of patients received IFN 0.5 million units subcutaneously twice daily, and the other half were given IFN 5 million units subcutaneously once a day.

The two groups had similar response rates. The median progression-free survival time was 3.7 months with the twice-daily lower dose and 3.4 months in the once-daily intermediate dose. The median overall survival time was 25.5 months for the twice-daily group of patients and 17.5 months for the once-daily group. It is worth noting that more than twice as many patients who received the intermediate dose scored above the clinical cutoff point for depression after eight weeks of treatment.

(Source: Cancer 2006;107:2254–2261.)

**A Link between Urinary Stones and Atazanavir?**

Indinavir sulfate (Crixivan, Merck) has been shown to cause urinary stones, but other protease inhibitors have not been associated with the same problem. Researchers from Hôpital Saint-Antoine in Paris, however, reported on what might be the first case of urolithiasis induced by atazanavir (Reyataz, Bristol-Myers Squibb).

Their patient, a 38-year-old man, was diagnosed with human immunodeficiency virus (HIV-1) infection in 2003. At the time, he was being treated for liver cirrhosis caused by hepatitis B virus. He also had a history of urinary calcium oxalate stones.

He was prescribed antiretroviral treatment with didanosine (Videx, Bristol-Myers Squibb), tenofovir (Truvada, Gilead), and efavirenz (Sustiva, Bristol-Myers Squibb), but because of neurological adverse effects, he was switched to emtricitabine (Emtriva, Gilead), tenofovir, and ritonavir (Norvir, Abbott)-boosted atazanavir 100/300 mg/dl.

Over the course of about six months,
he began having attacks of renal colic approximately once a month, then every two weeks. Nonsteroidal anti-inflammatory drugs (NSAIDs) and urinary alkalinization were not helpful. Renal ultrasonography revealed calculi in the right kidney. Ureteroscopic stone extraction and double-J urethral stenting were performed in June 2006. Spectrophotometry of two calculi showed they were composed of pure atazanavir.

Indinavir tends to crystallize in alkaline urine, leading to renal colic in approximately 8% of patients, the researchers note. Such crystallization has not been reported with atazanavir, although the product information lists renal colic as a rare adverse event.

As with indinavir, the solubility of atazanavir is increased in acid fluids. In this patient, the researchers suggest, impaired hepatic metabolism may have led to increased renal elimination of atazanavir, favoring its crystallization.

(Source: AIDS 2006;20:2131.)

**Sodium Bicarbonate Accelerates Paracetamol Absorption**

Paracetamol with sodium bicarbonate is absorbed at least twice as fast as a standard paracetamol tablet, say researchers who conducted a study at Unidad de Farmacología Clínica in Mexico. Paracetamol, a pain medication, is known as acetaminophen in the U.S.

The study was designed to mimic the actual use of over-the-counter analgesics. Researchers gave 30 healthy volunteers a 500-mg dose orally of either formulation along with 50 ml of water two hours after a breakfast of one fried egg, a slice of bacon, a slice of toast with butter and marmalade, hash-browned potatoes, and whole milk. It is recommended that 1 g of paracetamol/sodium bicarbonate be taken with 100 ml of water. The resulting concentration of sodium bicarbonate in the stomach is approximately isotonic, which is believed to enhance gastric emptying. In this study, 50 ml of water produced the same sort of isotonic concentration. In the fasting state, the researchers say, the influence of sodium bicarbonate on gastric emptying may be more pronounced.


**Long-Term Effects of Dexamethasone**

Bacterial meningitis can lead to cognitive impairment, even after a full recovery. Dexamethasone (Decadron, Merck)—which has become routine treatment for the infection—has been associated with long-term cognitive side effects. However, researchers from the University of Amsterdam say the concern is unwarranted.

They examined the potential harmful effects of adjunctive dexamethasone on long-term cognitive outcomes in 99 patients with pneumococcal or meningococcal meningitis. Of those patients, 87 were included in the follow-up: 46 received dexamethasone, and 41 received placebo.

Neurological examinations at a median of eight years after discharge (30 to 146 months) revealed that 17 patients (20%) had cognitive impairment.

Of 38 patients (21%) who had had pneumococcal meningitis, eight had cognitive dysfunction, compared with three of 49 patients (6%) who had had meningococcal meningitis. However, no differences were found between the treatment groups.

The researchers say that their study comprised the largest number of patients who had been evaluated to date over a long term. Their findings suggest that neuropsychological impairment improves in the first years after bacterial meningitis and becomes relatively stable with time.

(Source: Ann Neurol 2006;60:456–468.)

**Warning Added to Aprotinin Label**

The FDA has approved revised labeling for aprotinin injection (Trasylol, Bayer) to strengthen its safety warnings and to limit its approved usage. This medication is indicated for patients before heart surgery to reduce bleeding and the need for blood transfusions.

The new labeling specifies that this agent should be given only to patients who are at an increased risk for blood loss and blood transfusion in the setting of coronary bypass graft surgery when patients undergo cardiopulmonary bypass. The changes also mention that aprotinin may increase the risk of kidney damage. The FDA began this safety review in January 2006.

(Source: FDA, December 18, 2006, www.fda.gov.)

**Torcetrapib Trials Halted**

On December 2, 2006, the FDA was notified that Pfizer would be suspending a large phase 3 trial designed to evaluate a combination therapy consisting of torcetrapib and atorvastatin (Lipitor, Pfizer) to lower the risk of cardiovascular disease. Pfizer stopped the study because of an increased mortality rate in patients receiving the combination compared with those receiving atorvastatin alone. The FDA will continue to work with Pfizer and other sponsors developing molecules in this class of drugs to ensure that appropriate protections are in place to identify any safety signals as early in the development process as possible.

Clinical trial data on torcetrapib are presented in the American Heart Association Meeting Highlights feature on page 48.

(Source: FDA, December 4, 2006.)

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New Screening Test For Blood Donors

The FDA has approved a new test to identify blood donors who might be infected with a blood-borne parasite that causes Chagas’ disease, a potentially fatal parasitic infection. The Ortho T. cruzi ELISA Test System (Ortho-Clinical Diagnostics) detects antibodies to the Trypanosoma cruzi parasite, and it is the first such test approved by the FDA.

As many as 11 million people may have T. cruzi infection, most commonly in Mexico and Central and South America. The infection can be acquired from the bite of an infected insect or through blood transfusions or organ transplants. Infection can be severe in people with suppressed immune systems, such as organ transplant recipients.

Concerns about the potential for transmission and organ-transmitted Chagas’ disease in the U.S. have grown because of the increase in the number of U.S. residents who previously lived in countries where the infection is common.

In studies reviewed by the FDA, the test was accurate 99% or more of the time. In field trials, the number of false-positives was extremely small (2 or 3 out of 100,000 test results).

The test can also be used to screen plasma and serum samples from organ, cell, and tissue donors.

(Source: FDA, December 19, 2006.)

New FDA Chief Confirmed

The Senate confirmed Dr. Andrew C. von Eschenbach, 65, as commissioner of the FDA on December 7 after the abrupt resignation of Dr. Lester Crawford. He previously had served as chief academic officer at the M.D. Anderson Cancer Center in Houston, and he had also led the National Cancer Institute.

Dr. von Eschenbach believes that new drugs should be made available as quickly as possible, particularly medications for life-threatening illnesses.

The new chief was formally nominated to the position of commissioner in September 2005 after the abrupt resignation of Dr. Lester Crawford. He previously had served as chief academic officer at the M.D. Anderson Cancer Center in Houston, and he had also led the National Cancer Institute.

Dr. von Eschenbach succeeds Dr. Crawford, who resigned from the post after questions about discrepancies in his financial disclosure forms.

(Source: The New York Times, December 8, 2006.)

NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: 36-mm Zenith Flex AAA Endovascular Graft

Manufacturer: Cook, Inc., Bloomington, IN

Approval Date: October 31, 2006

Use Classification: The graft is indicated for the treatment of abdominal aortic aneurysms (AAAs).

Description: This device offers an endovascular solution for the interventional treatment of AAAs in patients with a large abdominal aortic neck diameter (range, 29 to 32 mm).

Purpose: AAAs can be life-threatening. When a section of the abdominal aorta, the body’s main circulatory vessel, weakens and bulges outward, an aneurysm is formed. If the aneurysm ruptures, the patient is at high risk of death as a result of internal bleeding.

The aortic endograft’s design and the accompanying 22 French H&L-B One-Shot Introduction System with Flexor Sheath and Captor Hemostatic Valve offer physicians an option for patients who might otherwise be untreatable.

Benefit: The endograft is designed to be minimally invasive for certain patients who might not have been candidates for endovascular aortic repair.

Source: www.cookmedical.com

Name: Diagnosoft Harmonic Phase (HARP) Cardiac MRI Quantitative Regional Function Software

Manufacturer: Diagnosoft, Inc., Lutherville, MD

Approval Date: November 15, 2006

Use Classification. The software assists physicians in analyzing magnetic resonance images (MRIs) by providing measurements and visualization of regional heart function. The algorithm automatically generates cardiac bulls-eye diagrams of myocardial strain and depicts regions of deprived myocardial function.

Description: With this software, images can automatically be analyzed and measures can be visualized on a standard.

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standard map designed to help physicians correlate abnormalities with coronary arteries that might be blocked.

**Purpose:** This computer-assisted tool displays relevant information about cardiac performance. This product is the first FDA-approved software designed for the analysis of “tagged” MRIs. Tagging aids in tracking the motion of objects, and it is valuable in cardiac imaging because the tissue in the walls of the heart provides few natural features for motion tracking.

**Benefit:** Robust image-analysis methods applied to tagged MRIs allow cardiologists and radiologists to measure and visualize cardiac muscle performance at a level that has not been possible before. More information can lead to more specific diagnoses via noninvasive imaging, which is more efficient for clinicians and safer for patients.

**Sources:** www.pharmacyonesource.com; www.diagnosoft.com; Johns Hopkins Image Analysis and Communications Lab, http://iacl.ece.jhu.edu

**Name:** Syngo Lung Computer-Aided Detection Program

**Manufacturer:** Siemens Medical Solutions, Malvern, PA

**Approval Date:** November 17, 2006

**Use Classification:** This software is designed to detect lung nodules in computed tomography (CT) examinations of the chest.

**Description:** The device includes proprietary image-processing and pattern-recognition algorithms that have been extensively trained on a large database of thoracic CT studies.

**Purpose:** The program is designed to detect a range of lung nodule sizes, starting at 3 mm in diameter.

**Benefit:** The detected nodules cover the full range of locations and contours, and the software works equally well in the presence or absence of intravenous contrast. The growth rate and nodule size of detected nodules can easily be compared by automated alignment and volume calculation, thus supporting the physician’s treatment regimen.

**Sources:** www.pharmacyonesource.com; www.fda.gov/cdrh/nda/docs/p050022.html

**Device Alert**

A meta-analysis performed at the Cleveland Clinic revealed as much as a four-fold to five-fold increased relative risk for late blood clot formation in patients with implanted drug-eluting stents, compared with patients with bare-metal stents. However, the researchers advised that this doesn’t mean that the stents should not be used. Other studies, they say, indicate that the drug-coated stents can reduce the need for repeated procedures when compared with bare-metal stents.

In another study, patients receiving the drug-eluting devices experienced a doubling of their risk of a heart attack or heart-related death after they stopped taking the anticlotting medication clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi), compared with patients who received bare-metal stents.

The FDA may recommend stricter testing standards for new cardiac stents to ensure that the devices are safer than those now available, and the agency is developing new guidelines.

Stent makers, including Johnson & Johnson and Boston Scientific Corporation, may be asked to show whether drug coatings will split away from the metal structures of the devices. Such a failure might allow a diseased artery to close off again, potentially causing chest pain or a heart attack.


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