**NEW DRUGS**

### Galsulfase for Mucopolysaccharidosis VI
BioMarin Pharmaceutical has announced that the U.S. Food and Drug Administration (FDA) has granted marketing approval for galsulfase (Naglazyme™), the first therapy indicated for the treatment of mucopolysaccharidosis VI (MPS VI). Naglazyme™ has been granted orphan drug status in the U.S.

MPS VI (also known as Maroteaux–Lamy syndrome) is a debilitating, life-threatening genetic disease caused by a deficiency of the enzyme N-acetylgalactosamine 4-sulfatase.

Naglazyme™ improved walking and stair-climbing capacity, as demonstrated by the 12-minute walk test and the three-minute stair climb. The drug reduced the excess carbohydrates that are excreted in the urine of patients with MPS VI, an indication of enzymatic bioactivity.

(Source: BioMarin, June 1, 2005; www.mpsvi.com.)

### Whooping Cough Vaccine
A new vaccine offers a single booster immunization against pertussis (whooping cough), in combination with tetanus and diphtheria, for adolescents and adults 11 to 64 years of age. The vaccine will be marketed as Adacel™ by Aventis Pasteur, Ltd., in Toronto, Canada.

This is the first vaccine approved as a pertussis booster for adults. Vaccines for the prevention of tetanus and diphtheria (Td vaccine) in adolescents and adults have been available for many years. The product is a tetanus toxoid (T), reduced diphtheria toxoid (d) and acellular pertussis vaccine (ap), adsorbed. It contains the same components as Daptacel® (Aventis Pasteur), a DTaP vaccine for infants and children, but the diphtheria toxoid and one of the pertussis components are in reduced quantities.

The FDA recently approved a similar vaccine, Boostrix™ (GlaxoSmithKline), for adolescents.

(Source: FDA, June 10, 2005.)

### Tigecycline, A First-in-Class Antibiotic
The FDA has approved tigecycline (Tygacil™, Wyeth), an intravenous antibiotic with a broad spectrum of antimicrobial activity against methicillin-resistant Staphylococcus aureus (MRSA) to treat complicated skin and skin-structure and intra-abdominal infections in adults.

This is the first antibiotic approved in a new class called glycylcyclines, which overcome key mechanisms of resistance that have affected antibiotic use.

For more information on tigecycline, please see the “Pharmaceutical-Approval Update” column on page 414 in this month’s issue of P&T.

(Source: Wyeth, June 15, 2005.)

### Sildenafil for Pulmonary Arterial Hypertension
Sildenafil citrate (Revatio™, Pfizer) has been approved as a treatment for pulmonary arterial hypertension (PAH), a rare, aggressive, and life-shortening vascular disease. Sildenafil citrate is the active ingredient in Viagra®, Pfizer’s medication for erectile dysfunction.

PAH is characterized by dangerously high pressure in the blood vessels that lead from the heart to the lungs.

The FDA’s approval was based on the results of a randomized, double-blind, placebo-controlled study that measured the exercise capability of patients after 12 weeks of treatment.

Revatio™ is the first oral treatment for PAH to be approved for patients with early-stage disease.

The use of Revatio™ or Viagra® and organic nitrates in any form, at any time, is contraindicated.

(Source: Pfizer, June 6, 2005.)

### Generic Paraplatin® Approved
Spectrum Pharmaceuticals, Inc., has announced the approval of its Abbreviated New Drug Application (ANDA) for carboplatin injection in 50-, 150-, and 450-mg multidose vials from the FDA’s Office of Generic Drugs. Carboplatin is a platinum-based, anti-cancer drug used in the treatment of patients with various tumor types. Paraplatin® is marketed by Bristol-Myers Squibb.

In April, Spectrum entered into an alliance with Cura Pharmaceuticals Co., Inc., to market and distribute carboplatin injection in the U.S.

(Source: Spectrum, June 14, 2005.)

### Insulin Analogue for Diabetes
Novo Nordisk has announced the FDA’s approval of Levmir®, a soluble, long-acting (basal) human insulin analogue for the treatment of diabetes. This agent has already been approved for use in 37 countries.

This analogue has a relatively flat action profile with a prolonged duration of action of up to 24 hours. It is indicated for once-daily or twice-daily subcutaneous administration for adults with diabetes mellitus who require basal insulin to control hyperglycemia.

The FDA is expected to decide on its use in children before the end of 2005.

(Source: Novo Nordisk, June 17, 2005.)

### Tipranavir for HIV Infection
The FDA has granted accelerated approval of tipranavir (Aptivus®, Boehringer Ingelheim) capsules for patients with human immunodeficiency virus-1 (HIV-1) infection. Longer-term data will be needed before traditional approval can be considered.

The approved dose is 500 mg taken with 200 mg of ritonavir twice daily in order to boost therapeutic levels of tipranavir; otherwise, tipranavir levels...
would be insufficient to inhibit replication of the virus.

Tipranavir inhibits HIV replication for many strains of the virus that have been resistant to other protease inhibitors. It does not cure HIV infection or AIDS and does not prevent HIV transmission.

(Source: Boehringer Ingelheim, June 23, 2005.)

**Heart Failure Drug For African-American Patients**

BiDil® is now approved for the treatment of heart failure in self-identified African-Americans. The approval was based partly on results from the African-American Heart Failure Trial (A-HeFT).

Patients receiving BiDil® experienced a 43% reduction in death and a 39% decrease in hospitalization for heart failure, compared with rates for placebo, and decreased symptoms of heart failure.

The product contains two older drugs, neither of which has been approved for heart failure—hydralazine (Apresoline®, Novartis) and isosorbide dinitrate (e.g., Sorbitrate®, AstraZeneca).

As an anti-hypertensive agent, hydralazine relaxes the arteries, and decreases the work of the heart. The anti-anginal agent, isosorbide dinitrate, relaxes the veins and arteries. Isosorbide seems to work by releasing nitric oxide at the blood vessel wall, but its effect usually wears off after half a day. Hydralazine may prevent this loss of effect. How the two drugs work together is not yet clear.

(Source: NitroMed, June 23, 2005.)

**NEW INDICATIONS**

**Pregabalin For Partial-Onset Seizures**

Pregabalin (Lyrica™, Pfizer) has been approved as an adjunctive treatment of partial-onset seizures in adults with epilepsy.

The efficacy of pregabalin was established in three double-blind, controlled trials involving 1,052 patients. At the start of treatment, patients were having approximately 10 seizures a month even though they were taking one to three other antiepileptic medications. Patients receiving adjunctive therapy with pregabalin experienced a reduction in the frequency of partial seizures by up to 51%.

The recent approval of fondaparinux for patients undergoing abdominal surgery was based on the results of the Pentasaccharide General Surgery Study (PEGASUS).

(Source: GlaxoSmithKline, May 27, 2005.)

**Nitazoxanide for Cryptosporidium-Related Diarrhea**

The FDA has approved nitazoxanide tablets and oral suspension (Alinia®, Romark Laboratories) for treating diarrhea caused by *Cryptosporidium parvum* infection in adults and children 12 years of age and older. The product is already approved to treat this infection in younger children.

For adults and teenagers, this is the first treatment for infections caused by the water-borne protozoan. Infection is typically spread by person-to-person contact or through contaminated water or food.

In a recent study, nitazoxanide significantly reduced the duration of diarrhea and other gastrointestinal symptoms when it was compared with a placebo. Ninety-six percent of patients treated with the tablets and 87% of patients treated with the suspension were well within seven days after beginning treatment; only 41% of patients who received a placebo recovered within this time frame. All patients receiving the study drug completed their treatment.

Afinia® is now indicated for the treatment of diarrhea caused by *Giardia* or *Cryptosporidium* in patients one year of age and older.

(Source: Romark, June 16, 2005.)

**NEW FORMULATION**

**Paricalcitol Reduces Secondary Hyperparathyroidism**

Abbott Laboratories has announced the FDA’s approval of paricalcitol (Zemplar®) capsules, an activated vitamin D therapy for prevention and treatment of secondary hyperparathyroidism (SHPT) in stage 3 and 4 chronic kidney disease before dialysis or transplantation is needed.
SHPT is a major complication associated with renal disease that can adversely affect bones and other vital organs, including the heart, muscles, and nerves, if left untreated. It can occur when kidneys lose their ability to activate vitamin D obtained through the diet and other sources.

This is a new oral formulation of Zemplar® Injection, which was introduced in 1998. The capsules were designed to reduce parathyroid hormone (PTH) levels with minimal effect on calcium and phosphorus levels.

PTH, calcium, and phosphorus levels should be monitored every three months and more often during dosage changes. Excessive administration of vitamin D compounds can cause oversuppression of PTH, hypercalcemia, hypercalciuria, hyperphosphatemia, and adynamic bone disease.

(Sources: Abbott, May 27, 2005; www.zemplar.com.)

Extended-Release Therapy For ADHD

Novartis has announced the approval of extended-release dexmethylphenidate HCl (Focalin XR™) for adults, adolescents, and children with attention-deficit/hyperactivity disorder (ADHD), a neurobiological disorder. ADHD interferes with the ability to regulate activity level and behavior and to sustain focus in developmentally appropriate ways.

This product is an extended-release form of Focalin®, a refined formulation of Novartis’ drug Ritalin® (d,l-methylphenidate HCl). Whereas Ritalin® contains both the d- and l-isomers of methylphenidate, Focalin® contains only the more active d-isomer. The l-isomer, which is essentially inert, is left out. Consequently, the usual dose of Focalin® is half that of Ritalin®.

Focalin XR™ is available in 5-, 10-, and 20-mg capsules and is taken once daily.

(Sources: Novartis, May 27, 2005; www.FocalinXR.com; www.centerwatch.com.)

Defibrillators Recalled

Guidant Corporation says that its implanted cardiac defibrillators (ICDs), used by 50,000 heart patients, might be flawed. The company has offered to replace more than half of them. At least two patients have died.

The potential flaw cannot be fixed without removal of the ICDs. The recall includes the Contak Renewal and Renewal 2, Ventak Prizm AVT, Vitality AVT, Renewal 3 AVT, and Renewal 4 AVT ICDs.

A programming change can be made for some of the devices in the doctor’s office to reduce the risk of a short circuit.

(Source: The Philadelphia Inquirer, © Associated Press, June 18, 2005.)

Cancer Drug to Be Restricted

The FDA plans to allow only a few thousand patients with lung cancer to continue using gefitinib (Iressa™, AstraZeneca) because it has not lived up to its promise.

Patients with advanced lung cancer who believe the drug is helping them will not lose access to it, but after September 15, the drug will be sold only through one mail-order pharmacy. Special documentation of eligibility will be required by physicians and patients.

Iressa™ was one of the first targeted cancer therapies. Some terminally ill patients lived longer than expected with the drug, but only about 10% of patients responded to it.

A possible explanation is that Iressa™ targets a specific molecule that spurs growth of lung cancer cells, but it seems to work only in patients whose tumors have a certain gene mutation that is more common among nonsmokers, women, and Japanese patients.

The restricted access applied only to sales in the U.S.

(Sources: The Philadelphia Inquirer, The Boston Globe, © Associated Press, June 17, 2005.)

Sildenafil Label and Vision Loss

Pfizer has agreed to change the label for Viagra® (sildenafil), its medication for erectile dysfunction, to warn doctors about sudden vision loss in some men who took the drug.

The FDA is asking all makers of impotence drugs to include similar warnings. No "causal relationship" has been made between Viagra® and the condition, a type of eye stroke called non-arteritic anterior ischemic optic neuropathy, Pfizer said.

Pfizer released its statement before a CBS News report that examined four years of FDA data on complications among Viagra® users. The analysis found 800 reports of eye problems, including 140 cases of partial or total blindness, CBS said. Pfizer said its own review found no evidence of increased risk of blindness in men taking the drug.

(Source: Bloomberg News, June 27, 2005.)

Fatigue and Warfarin

Patients taking warfarin (Coumadin®, Bristol-Myers Squibb) often report that they feel tired, and this may make it more difficult for them to adhere to long-term treatment. However, it might not be the warfarin that is causing low energy, say researchers from the Canadian Institutes of Health.

In a substudy of a double-blind trial in 13 outpatient thromboembolism clinics, patients who had received a one-month trial of open-label warfarin therapy for venous thromboembolism caused by a transient risk factor were randomly assigned to receive warfarin or placebo for two months. They were observed for continued on page 382.
another nine months after they stopped taking the study drug.

Thirty-nine patients were randomly assigned to continue taking warfarin for two months, and 48 were assigned to receive placebo. Patients used a seven-point Likert Scale to rate their fatigue.

Overall, the researchers found no association between warfarin and fatigue. By the end of the study, the patients’ overall ratings of fatigue were 0.1 unit lower. Their global ratings for change of intensity of fatigue at two months and 11 months also showed a significant reduction over time and no association between increased fatigue and warfarin use.

(Source: Ann Pharmacother 2005;39: 840–842.)

Aspirin before Coronary Bypass Surgery

It appears that taking aspirin before coronary artery bypass graft surgery (CABG) can lead to a shorter stay in the intensive-care unit (ICU) by helping to protect the lungs against complications, say researchers from Israel. They studied 32 patients, 14 of whom received aspirin until the day of the operation and 18 who stopped aspirin at least one week earlier.

Better oxygenation and shorter ventilation times were two advantages of giving aspirin to patients who were about to undergo CABG. The mean ventilation time was significantly shorter in the aspirin group (3.8 vs. 9.6 hours). The partial pressure of oxygen in arterial blood (PaO₂) reached a maximum of 235 mm Hg in the patients taking aspirin and 176 mm Hg in the controls. The minimal value of PaO₂ was 90 mm Hg with aspirin and 76 mm Hg with placebo.

Although surgery took 24 minutes longer in the aspirin patients because of the extra time needed for meticulous hemostasis, the effect of hemodilution or hemoconcentration, which can alter the extravascular fluid volume state, was negligible. No significant differences in fluid infusion and urine output were observed in the two groups of patients.

Although the aspirin patients experienced more total drainage through the chest tubes, the need for blood and blood products was similar in both groups. No significant difference was seen in hemoglobin levels at hospital discharge.

The total hospital length of stay was the same in both groups, but the aspirin patients needed less time in the ICU. The difference was only a few hours, but the researchers emphasized that the longer the ICU stay, the greater the potential for ICU-related complications.

(Source: Chest 2005;127:1622–1626.)

Abrupt Clonidine Withdrawal: A Cause of Heart Problems?

Studies show that catecholamine levels begin to rise within 24 hours of stopping the antiadrenergic agent clonidine (e.g., Catapres®, Boehringer Ingelheim). That can be a problem, as shown in a case study of a patient who had a heart attack after acute clonidine withdrawal.

At the University of Southern California Medical Center in Los Angeles, an 86-year-old woman arrived in the emergency department with a three-hour history of headache, nausea, vomiting, and severe precordial chest pain. She had been taking twice-daily clonidine for hypertension until about 36 hours before admission. For an unknown reason, her doctor had advised her to stop taking the clonidine. She was also taking clonazepam (e.g., Klonopin®, Roche).

The electrocardiogram (ECG) showed evidence of an evolving anterolateral myocardial infarction. She was given labetolol (e.g., Normodyne®, Key) and diazepam (Valium®, Roche). Within 10 minutes, her blood pressure dropped from 230/150 to 109/66 mm Hg, and her pulse slowed from 140 to 103 beats/minute. Her headache was gone. She was then given clopidogrel (Plavix®, Bristol-Myers Squibb/Sanoﬁ) and heparin. Two hours after her arrival, cardiac catheterization showed patent coronary arteries and no evidence of narrowing. She had severe left ventricular dysfunction.

After a stable hospital course, clonidine was restarted and her blood pressure was well controlled. At six months, she was symptom-free with no episodes of angina or congestive heart failure. Her ECG was normal except for first-degree atrioventricular block.

An editorial comment cautions that clonidine should never be stopped without first tapering the dose.


Are Drug-Eluting Stents As Successful as Reported?

The first 30 days after percutaneous coronary interventions are traditionally regarded as the window for stent thrombosis. Drug-eluting stents have reduced the risk, but outside of clinical trials, little is known about their long-term risk of stent thrombosis after that 30-day window has closed.

Researchers from Germany and Italy, conducting a study of 2,229 patients who underwent successful implantations, found a 1.3% incidence of stent thrombosis at nine months: in nine of 1,062 patients with sirolimus-eluting stents and in 20 of 1,167 patients with paclitaxel-eluting stents. Thirteen patients died.

Four sirolimus patients and 10 paclitaxel patients had subacute thrombosis, and five sirolimus and 10 paclitaxel patients had late thrombosis. Half of the late thrombosis cases (eight of 15) occurred within three months (median, 57 days).

A 1.3% rate may seem low, but this figure is substantially higher than the rates...
Less Medication for Asthma?

Adults with mild persistent asthma may be able to control attacks by taking corticosteroids only when needed, instead of taking anti-inflammatory drugs daily, according to the Improving Asthma Control Trial (IMPACT).

Conducted by the National Heart, Lung, and Blood Institute’s Asthma Clinical Research Network, the one-year, multicenter study found that participants who took corticosteroids when symptoms were present had rates of severe exacerbations and declines in asthma-related lung function that were similar to those of patients using daily long-term control medication.

The new findings might not apply if asthma has developed recently or if patients have more frequent symptoms or more severe asthma. The updated guidelines are to be released in 2006.


NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: Reliant Stent Graft Balloon Catheter

Manufacturer: Medtronic, Inc., Minneapolis, MN

Approval Date: June 7, 2005

Use Classification: This multipurpose catheter may be used during thoracic aortic aneurysm (TAA) repair, and it offers physicians more flexibility during endovascular aortic aneurysm repair (EVAR).

Description: The catheter has a working range of between 10 and 46 mm, the largest range of inflation diameters among the stent-graft balloon...
catheters on the market. The balloon is composed of a latex-free, polyurethane material. The usable catheter length is 100 cm long.

**Purpose:** The catheter is used to seal endoleaks by expanding the stent graft, removing debris from the graft material, and temporarily occluding blood flow in large vessels during EVAR.

**Benefit:** The balloon catheter also offers the lowest profile of all compliant balloons with an 8 French shaft, and it is compatible with a minimum 12 French introducer sheath.

**Source:** www.pharmacyonesource.com

**Name:** Zeno “Zit Zapper”

**Manufacturer:** Crutchfield Dermatology, Eagan, MN

**Approval Date:** June 3, 2005

**Use Classification:** Zeno is best suited for treating newly emerging blemishes, especially when they are forming under the skin.

**Description:** This portable, hand-held, rechargeable, nonprescription medical device is not a medication or a laser. It applies a controlled heat dose directly to individual blemishes in people with mild-to-moderate acne.

**Purpose:** The device destroys bacteria and shortens the life cycle of the lesion. It also appears to increase blood flow in the area of the blemish and promotes faster healing.

**Benefit:** Zeno delivers a dose of heat to the area for 2.5 minutes. It is recommended that blemishes be treated two to four times, at least one hour apart, over the first four to 12 hours of their appearance. In an FDA-reviewed clinical trial, 90% of patients found that pimples caught early and treated with this device faded or disappeared within 24 hours. Zeno should not replace normal skin-care programs. It is totally compatible with other acne-treatment programs.

**Sources:** www.pharmacyonesource.com; http://crutchfielddermatology.com

**Name:** Rithron-XR Coronary Stent System

**Supplier:** Biotronik GmbH, Berlin, Germany

**Approval Date:** April 29, 2005

**Use Classification:** This stent system is indicated for patients with narrowed coronary arteries caused by atherosclerosis, the collection of fatty substances (e.g., cholesterol) that forms plaque along the arterial lining.

**Description:** The stent, an expandable, slotted, stainless steel tube, is mounted over a deflated balloon attached to the end of a long, thin, flexible tube (the stent delivery catheter). Gold markers on the stent help the surgeon place the device in an artery. The stent and markers are coated with silicon carbide. The stent is permanently implanted within the coronary artery, acting as a scaffold, or support, for the newly opened section of vessel.

**Purpose:** A catheter with a deflated balloon at its tip is inserted into a blood vessel in the arm or groin. It is then advanced within the vessel to the narrowed section of the coronary artery. The balloon is inflated within the narrowed artery; this opens the artery by pushing the plaque against the artery wall balloon angioplasty. The angioplasty balloon and its catheter are withdrawn from the patient. The stent is mounted on another deflated balloon catheter (the stent-delivery catheter), advanced through the same vessel, and positioned within the expanded coronary artery. The balloon on the stent-delivery catheter is inflated, causing the stent to expand to the size and contours of the vessel. This restores the opening in the artery, allowing normal blood flow to the heart. The balloon is then deflated, and the delivery catheter—without the stent—is removed. The stent remains in place permanently.

**Precautions:** The stent should not be used in patients in whom antiplatelet or anticoagulant therapy is contraindicated; who might have a lesion that prevents complete inflation of an angioplasty balloon; and who have allergies to stainless steel, gold, or silicon carbide.

**Benefits:** Expansion of the stent within the narrowed section of a coronary artery allows more blood flow to the heart. If the narrowing is not treated, a heart attack or even death can occur.

**Source:** www.fda.gov

**Name:** PAXgene™ Blood RNA System

**Manufacturer:** PreAnalytiX GmbH, Becton, Dickinson and Co. Franklin Lakes, NJ

**Approval Date:** April 18, 2005

**Use Classification:** The PAXgene™ system is used to collect a patient’s blood sample and to isolate ribonucleic acid (RNA) for use in diagnostic laboratory tests. RNA translates genetic information from DNA to proteins produced by the cell.

**Description:** The system comprises a plastic tube for collecting blood and a kit for purifying nucleic acid from a patient’s blood sample. The tube contains chemicals that can stabilize RNA from cells in the blood sample to keep the RNA intact for shipment at room temperature or storage for a short time at room temperature or in the refrigerator. The stabilized RNA is separated from other substances in the blood with the purification kit.

**Purpose:** The RNA that is obtained can be used for reverse transcriptase–polymerase chain reaction in vitro molecular diagnostic laboratory tests.

**Benefit:** RNA can be used to help confirm or rule out a suspected disease.

**Source:** www.fda.gov