NEW DRUGS

Insulin Glulisine and Insulin Detemir for Diabetes

The Food and Drug Administration (FDA) has approved insulin glulisine (rDNA origin) injection (Apidra, sanofi-aventis) for the control of hyperglycemia in adults with type-1 and type-2 diabetes. This insulin analogue can be taken within 15 minutes before or within 20 minutes after starting a meal. It should be used in regimens that include a longer-acting insulin or a basal insulin analogue such as insulin glargine (Lantus, Aventis).

Insulin glulisine has a more rapid onset of action and a more flexible dosing schedule than regular human insulin.

Because of this agent’s short duration of action, patients will also need a longer-acting insulin or insulin infusion pump therapy to maintain adequate glucose control.

Levemir is available in vials and in a prefilled disposable pen.

The drug offers up to 24 hours of blood glucose control. In a clinical trial, 70% of treated patients achieved targeted glycosylated hemoglobin levels below 7%. This is the first basal insulin analogue marketed in the U.S. It is indicated once or twice daily for adults and children with type-1 diabetes and for adults with type-2 diabetes.

The drug offers up to 24 hours of blood glucose control. In a clinical trial, 70% of treated patients achieved targeted glycosylated hemoglobin levels below 7%. This is the first basal insulin analogue marketed in the U.S. It is indicated once or twice daily for adults and children with type-1 diabetes and for adults with type-2 diabetes.

Levemir is available in vials and in a prefilled disposable pen.

* * *

Novo Nordisk Inc. has launched insulin detemir (Levemir, rDNA origin), a long-acting basal insulin analogue in the U.S. It is indicated once or twice daily for adults with type-1 diabetes and for adults with type-2 diabetes.

The drug offers up to 24 hours of blood glucose control. In a clinical trial, 70% of treated patients achieved targeted glycosylated hemoglobin levels below 7%. This is the first basal insulin analogue marketed in the U.S. It is indicated once or twice daily for adults and children with type-1 diabetes and for adults with type-2 diabetes.

Levemir is available in vials and in a prefilled disposable pen.

(Source: FDA; Novo Nordisk, March 28, 2006.)

Cetuximab for Head and Neck Cancer

Cetuximab (Erbitux) is now approved for use in combination with radiation therapy to treat patients with unresectable squamous cell cancer of the head and neck. It is manufactured by ImClone Systems and will be distributed and marketed by Bristol-Myers Squibb.

This is the first drug approved for head and neck cancer that has shown survival benefits for patients. It delayed tumor growth when used with radiation and helped shrink tumors after they no longer responded to platinum-based therapy.

Cetuximab is discussed in this month’s Pharmaceutical Approval Update: Oncology column, page 208.

(Source: cancerconsultants.com; FDA, March 1, 2006; N Engl J Med 2006; 354:567–578.)

Rituximab/Methotrexate For Rheumatoid Arthritis

Genentech, Inc., and Biogen Idec have announced the FDA’s approval of the therapeutic antibody rituximab (Rituxan) in combination with methotrexate (MTX) for adults with moderately to severely active rheumatoid arthritis (RA) who have not responded adequately to one or more tumor necrosis factor antagonist therapies. This is the first RA therapy that targets immune cells known as CD20-positive B cells.

Rituximab was approved in 1997 for patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell non-Hodgkin’s lymphoma. In February 2006, it was also approved for diffuse, large B-cell non-Hodgkin’s lymphoma in combination with CHOP chemotherapy or with other anthracycline-based chemotherapy. This drug is also being studied for other autoimmune diseases.

Rituximab is featured in this month’s Drug Forecast column on page 201.

(Source: Genentech/Biogen Idec, February 28, 2006.)

Generic Injectable Azithromycin

Baxter Healthcare Corporation has launched generic azithromycin for injection (Pfizer/Zithromax), a commonly used antibiotic. The launch marks the first time Baxter has been granted exclusive authorization by a pharmaceutical company to market a generic version of its brand product. Pfizer will manufacture the product, and Baxter will sell and market it in the U.S.

(Tentative Approval for Generic Zofran Injection

American Pharmaceutical Partners has received two tentative approvals from the FDA for its Abbreviated New Drug Applications (ANDAs) for Ondansetron Injection, USP, in single-dose and multiple-dose vials. As the generic equivalent of GlaxoSmithKline’s Zofran Injection, it is indicated for the prevention of postoperative and chemotherapy-related nausea and vomiting.

(Source: American Pharmaceutical Partners, March 9, 2006.)

24-Day Oral Contraceptive

Berlex, Inc., a U.S. affiliate of Schering AG, Germany, has announced the FDA’s approval of a monophasic oral contraceptive (Yaz). This is the first tablet to combine 20 mcg of ethinyl estradiol with 3 mg of the progestin drospirenone.

This 24-day regimen causes less hormonal fluctuation than traditional oral contraceptives providing a 21-day course.

In a large clinical trial, Yaz demonstrated an efficacy rate of 99%. The women experienced predictable monthly withdrawal bleeding, and most of them tolerated the medication well.

(Source: Berlex, March 17, 2006.)

NEW INDICATIONS

Selegiline Patch for Depression

The FDA has approved a selegiline transdermal system (Emsam), the first
patch for adults with major depressive disorder (MDD). Somerset Pharmaceuticals developed the drug, and Bristol-Myers Squibb will market it. Selegiline was approved in 1989 to treat Parkinson’s disease.

This drug is a monoamine oxidase inhibitor (MAOI). Consequently, the drug’s label will carry a black-box warning and a list of tyramine-containing foods and drinks that patients must avoid while using the patch.

The recommended starting dose is one 6-mg/24-hour patch administered once daily.

(Sources: Associated Press, February 28, 2006; Bristol-Myers Squibb/Somerset.)

Fluticasone for Young Children

The FDA has approved fluticasone propionate (Flovent, GlaxoSmithKline) in asthmatic children 4 to 11 years of age. This inhaled corticosteroid helps prevent inflammation in the airways, one of the main components of asthma.

Flovent HFA, a reformulation of Fluticasone for Inhalation Aerosol, uses hydrofluoroalkane (HFA-134a) to propel the medication out of the canister and into the lungs. Hydrofluoroalkane replaces the chlorofluorocarbon propellant and is a more environmentally friendly aerosol formulation.

Flovent HFA was first approved in May 2004 for patients 12 years of age and older. The dosage for children 4 to 11 years of age is 88 mcg twice daily.

(Source: GlaxoSmithKline, March 23, 2006.)

NEW FORMULATION

Extended-Release Tramadol

Once-daily tramadol HCl extended-release tablets (Ultram ER, Ortho-McNeil/Biovail) are now available by prescription in the U.S for patients with moderate to moderately severe chronic pain. This is the first extended-release form of tramadol for adults who require around-the-clock treatment of pain for an extended period of time. The tablets are available in strengths of 100, 200, and 300 mg.

Tramadol, a synthetic opioid analgesic, was introduced in the U.S. in 1995. The tablets should be swallowed whole, and the dose should not exceed 300 mg/day.

(Source: Ortho-McNeil/Biovail, February 21, 2006.)

DRUG NEWS

Antibiotic Cefazolin Recalled

Hanford Pharmaceuticals is voluntarily recalling four lots (379,975 vials) of Cefazolin for Injection, USP, 1 g/10-ml vials, an antibiotic used in hospitals to treat skin and skin structure, respiratory, and other infections.

Some lots of the product’s active ingredient were contaminated with Bacillus pumilus, Staphylococcus hominis, Propionibacterium acnes, or Micrococcus luteus. Such microbial contamination may be life-threatening for some patients.

The firm is asking customers to return the recalled lots (Sandoz lots C4650 and C4537 and Watson lots C4689, C4665). Hospitals and clinics should stop using the affected lots immediately. Patients or users can contact the firm at 315-476-7418. So far, Hanford has not received any confirmed reports of complaints related to the recalled lots.

(Source: Hanford, February 24, 2006.)

Emergency Bronchodilators Less Beneficial for Elderly

Researchers from Harvard University in Boston, Jewish General Hospital in Montreal, Summa Health System in Akron, and MetroHealth Medical Center in Cleveland have found that older patients may be less likely to benefit from bronchodilators in emergency departments (EDs).

In a study of 2,064 patients with asthma, all age groups had severe exacerbations. Patients 55 years of age and older, however, were least likely to report severe symptoms upon their arrival at the ED. Nonetheless, they received more inhaled beta agonists during their stay in the ED, were more likely to receive systemic corticosteroids and other asthma treatments, and had longer ED stays. Despite the more intense therapy, they showed the smallest change in peak expiratory flow.

Over the previous year, older patients made fewer urgent clinic and ED visits but were admitted to the hospital more often for asthma than younger patients. Patients in all age groups were equally likely to report severe symptoms upon their arrival at the ED. Nonetheless, they received more inhaled beta agonists during their stay in the ED, were more likely to receive systemic corticosteroids and other asthma treatments, and had longer ED stays. Despite the more intense therapy, they showed the smallest change in peak expiratory flow.

Over the previous year, older patients made fewer urgent clinic and ED visits but were admitted to the hospital more often for asthma than younger patients. Patients in all age groups were equally likely to report using the ED as their usual site of care for problematic asthma, but older patients were the least likely to receive their prescriptions in the ED.

The researchers suggest that older patients tend to use other drugs that can interact with bronchodilator therapy;
they have more comorbid conditions; aging affects the time course of drug absorption, distribution, and metabolism; and airway remodeling may lead to a poorer response.

Especially critical is the fact that more than half of the older patients were not taking inhaled corticosteroids, although 91% had a primary care provider. Research has shown that inhaled anti-inflammatory drugs and rescue corticosteroids are underused in older patients. Physicians may hesitate to prescribe inhaled corticosteroids because of concerns about adverse events, even though—as this study suggests—not using them can lead to poor asthma control and a more frequent need for hospital care.


**Antidepressants Help Treat Peripartum Blues**

Although pregnancy is generally considered to be a safe time during which hormonal changes protect women from psychiatric disorders, this is a myth, say researchers from Massachusetts General Hospital, the University of California, Los Angeles, and Emory University.

In a study of 201 pregnant women, 65 stopped antidepressant treatment around the time of conception; of those, 44 (68%) experienced relapses of depression during pregnancy. By contrast, 26% of 82 women experienced relapses while maintaining their antidepressant regimen. Approximately 50% of the women who stopped taking their medications had relapses in the first trimester, and 90% had relapses by the end of the second trimester.

The researchers suggest that reintroducing antidepressant therapy in the second trimester might be able to prevent the critical period of organogenesis. They warn that although this course attenuates the risk of depressive relapse a bit, women who restart treatment are still at higher risk for depression than those who sustain treatment.

(Source: JAMA 2006;295:499–507.)

**. . . But Do SSRIs Cause Harm to Infants’ Lungs?**

Expectant mothers who took antidepressants during late pregnancy were more likely to give birth to infants with a rare but potentially life-threatening breathing problem called persistent pulmonary hypertension (PPH).

An official at the FDA called the research results “very worrisome.” The agency will decide whether to require manufacturers to make labeling changes and conduct postmarketing studies to clarify the risk.

From 10% to 15% of pregnant women experience bouts of depression, and at least 10% of those take antidepressants. Up to one-third of fetuses exposed to antidepressants experience temporary withdrawal symptoms such as agitation. The FDA has warned that paroxetine (Paxil, GlaxoSmithKline), for instance, may increase the risk of rare heart problems in newborns exposed to the medication *in utero*.

The antidepressants included citalopram (Celexa, Forest); sertraline (Zoloft, Pfizer); paroxetine; and fluoxetine (Prozac, Eli Lilly). The researchers suggested that the drugs may hinder the body’s production of agents that help blood vessels dilate. If the vessels in a newborn’s lungs do not open properly, the infant cannot absorb sufficient oxygen and may may reflexively hold its breath, further starving itself of air. Giving an infant oxygen or nitric oxide, which helps open vessels, often relieves the problem. In 10% to 20% of cases, these infants need an artificial lung.

Pregnant women who are taking selective serotonin reuptake inhibitors (SSRIs) should consult their health care providers to decide how to proceed.


**More SSRIs, More Bleeding Risk**

As the number of prescriptions for SSRIs has increased, so have once-rare bleeding risks—a rise in risk that has been exacerbated by the greater concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs) and long-term antiplatelet regimens, among other factors.

A physician at Johns Hopkins Hospital has noted an increased frequency of bleeding complications and cautions about the possibility of SSRI-induced hemorrhages. All SSRIs exhibited antiplatelet properties, he emphasizes, and all have been implicated in bleeding episodes. Patients with even mild hereditary platelet defects are particularly at risk, as are those who are using antiplatelet drugs.

Most of the reports cited indicate a superficial site of bleeding events. More severe internal bleeding, including life-threatening cerebral hemorrhages, was rarer. Although most bleeding events were reported in adults, children have had such complications as well. Moreover [in addition to the risks discussed on this page], using SSRIs during pregnancy may also result in hematomas and other complications in newborns.


**‘Faster’ Anticoagulation For Cardioversion**

An “expedited” anticoagulation regimen for patients undergoing cardioversion appears to be safe, according to a recent study at the Mayo Clinic.

The minimum safe duration of intravenous (IV) heparin before transesophageal echocardiography-guided cardioversion of atrial fibrillation has been unclear—ranging from 1 to 4 days. In this study, researchers reported on a
regimen that shortened the duration of precardioversion IV heparin and, after successful cardioversion, sent patients home with prescriptions of low-molecular-weight heparin (LMWH).

One group of patients received IV heparin for as little as four hours or less; the other group received IV heparin for 24 hours or more. At one month, ADEs did not differ significantly between the two groups, and fewer than 1% of the 193 patients discharged with prescriptions for LMWH had strokes. No ADEs were seen among patients who received IV unfractionated heparin for less than 12 hours.

(Source: Am J Med 2006;119:142–146.)

Low-Dose Promethazine for Antiemesis without Sedation

Parenteral promethazine (Phenergan, Wyeth) is effective as an antiemetic agent, but it tends to exert significant sedative effects at the standard dosage of 25 mg, especially when it is used along with narcotic analgesics. Researchers at Anne Arundel Medical Center in Annapolis, Maryland, say that even a dose as low as 6.25 mg can still be effective.

At one hour, 33 of 46 patients taking low-dose promethazine had no nausea or vomiting, compared with 24 of 41 patients taking ondansetron (Zofran, GlaxoSmithKline) (4 mg). Only three patients in each group showed sedative effects.

(Source: Ann Pharmacother 2006;40: 45–48.)

Controlling Blood Glucose Improves Memory

Reducing fasting plasma glucose levels can improve memory in patients with diabetes, say researchers from University of Pittsburgh, who conducted a double-blind trial of 145 older adults with type-2 diabetes at 18 centers in the U.S. The patients were receiving metformin (e.g., Glucophage, Bristol-Myers Squibb) with add-on therapy consisting of rosiglitazone maleate (Avandia, GlaxoSmithKline) or glyburide (Diabeta, Aventis).

As expected, rosiglitazone, but not glyburide, was associated with improvements in circulating insulin and insulin sensitivity, but changes in insulin parameters did not affect cognitive function.

(Source: Diabetes Care 2006;29: 345–351.)

Will Natalizumab (Tysabri) for MS Return to the Market?

The Peripheral and Central Nervous System Drugs Advisory Committee of the FDA has voted unanimously to recommend the re-introduction of natalizumab (Tysabri, Biogen Idec/Elan) to the market for patients with relapsing multiple sclerosis (MS). The panel’s vote was based on the companies’ 3,000-patient safety evaluation, which revealed no additional cases of progressive multifocal leukoencephalopathy (PML) beyond the original two cases that led to the drug’s withdrawal from the market. PML is a rare but often fatal brain infection.

The FDA is studying whether the promising drug that carries this known and deadly side effect should be made available to some or all affected patients. The FDA will be considering how to balance the efficacy and safety of this medication. Sometimes a drug’s toxicity is deemed acceptable when the drug is found to be particularly beneficial. A decision is expected by June 28.

Natalizumab originally won accelerated approval from the FDA in November 2004. It was seen as a life-changing drug for patients with MS and as a potential blockbuster for its makers. Although it reduced the rate of MS relapses by 66%, sales were suspended just three months later. In February 2006, the drug was abruptly withdrawn after it was linked to the two cases of PML.

The FDA advisory panel stipulated that the drug should be returned to the market but should not be prescribed with other MS treatments. Some panel members called for a special doctor/patient registry for dispensing the drug.

Biogen Idec and Elan plan to re-launch human trials in Europe, the U.S., Canada, Australia, New Zealand, and Israel. The patients who took part in the previous phase 3 study, which was suspended last year, are eligible for enrollment in the re-initiated safety extension trial. Enrollment and dosing in the open-label trial have already begun.


Sepsis-Fighting Statins?

Statins exert multiple benefits, such as anti-inflammatory, immunomodulatory, and antithrombotic effects. An analysis of data from 69,168 patients with atherosclerosis in Ontario, Canada, suggests that statins might help reduce the risk of sepsis as well.

During a mean follow-up of two years, 551 patients who were given statins and 667 patients in the non-statin group were admitted for sepsis. Statins were associated with a 19% lower risk of sepsis. The apparent protective association was consistent for several high-risk subgroups throughout the entire follow-up.

Earlier research had suggested that statins substantially reduce inflammatory cytokines and the overproduction of nitric oxide, which is implicated in the vasodilation and circulatory collapse of septic shock, the researchers say. In addition to their effects on the host,
statins also seem to lessen the replication and infectivity of several bacterial, fungal, and viral pathogens.
(Source: Lancet 2006;367:413–418.)

Reducing Defibrillator Shocks With Drug Therapy

Shocks commonly occur after the first year that patients wear an implantable cardioverter defibrillator (ICD). Antiarrhythmic drugs such as amiodarone (Cordarone, Wyeth) and sotalol (Betapace, Berlex) can reduce both appropriate and inappropriate shocks in patients with ICDs, but how effective are these agents compared with standard beta-blocker therapy?

A multinational research team enrolled 412 patients with sustained or inducible ventricular tachycardia or ventricular fibrillation from 39 outpatient clinical centers worldwide in the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial. The patients were randomly assigned to take amiodarone plus a beta blocker, sotalol alone, or a beta blocker alone for one year. Sotalol was given alone because of its antiarrhythmic and beta-blocking effects. Of the 138 patients receiving beta blockers, 41 (39%) experienced shocks; shocks also occurred in 26 (24%) of 134 patients taking sotalol and in 12 (10%) of 140 patients taking amiodarone plus a beta blocker.

Both sotalol and amiodarone plus a beta blocker reduced the risk of the shocks compared with patients taking beta blocker therapy alone. Amiodarone plus a beta blocker significantly reduced the risk, whereas sotalol showed only a slight tendency toward reducing it.

Patients taking beta blockers were more likely to receive frequent shocks (more than 10 a year), as well as a first shock followed by another within 24 hours. At one year, however, only 5% of patients taking beta blockers had withdrawn from treatment, compared with 18% of the amiodarone patients and 24% of the sotalol patients.
(Source: JAMA 2006;295:165–171.)

Hurricane Katrina Victims Get Help with Medicare Part D

The Centers for Medicare & Medicaid Services (CMS) plans to grant all Hurricane Katrina evacuees more time to change their Medicare prescription drug plans in 2006.

Individuals are eligible for this plan if their residences are within certain zip codes, as identified by the Federal Emergency Management Agency (FEMA) at the time of the hurricane (August 2005). The evacuees will be able to switch plans, including Medicare Prescription Drug Plans, any time through December 31, 2006, if they change their residence, temporarily relocate, move back to their permanent home, or need more time to choose or change a plan. A list of eligible zip codes can be found at www.amcp.org and www.twelvehorses.com.
(Source: Academy of Managed Care Pharmacy, AMCP News, March 10, 2006.)

Medicare Part D Phone Scams

The federal government is warning Medicare Part D beneficiaries about a telephone scam in which they are being asked to supply checking account information. The scam is known as the “$299 Ring,” because that is the usual amount of money being forfeited to pay for a phony drug plan. The CMS warns that no legitimate Medicare Prescription Drug Plan can ask for bank account or other personal information over the phone. No one should be visiting their home uninvited, and no one should be asking for payment over the phone or via the Internet.
(Source: Academy of Managed Care Pharmacy, AMCP News, March 10, 2006.)

NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: UniCel DxC 600i Synchron Access Clinical System

Manufacturer: Beckman Coulter, Inc., Fullerton, CA

Approval Date: March 6, 2006

Use Classification: This system is designed to deliver standardized product lines with large on-board test menus for greater consolidation of workstations.

Description: With an on-board capacity of 89 reagents, the second-generation work cell offers more than 150 different tests, ranging from cardiac and tumor markers to assessments of renal function, diabetes, and other conditions.

Purpose: Clinical laboratories can perform both chemistry and immunoassay testing simultaneously from a single point of sample entry, thus resulting in increased productivity.

Benefit: This is the only system of its kind, with closed-tube sampling and closed-tube aliquot ring capabilities. By eliminating the decapping and recapping steps in the laboratory process, these features help increase efficiency and enhance operator safety. The system offers a throughput (a measure of the speed of data transmission) of up to 990 chemistry tests per hour and up to 100 immunoassay tests per hour.


Name: Vidar Vision

Manufacturer: Vidar Systems Corporation, Herndon, VA

Approval Date: March 2, 2006

Use Classification: The company’s digital radiography product line features continued on page 231
affordable systems for all radiography environments (e.g., imaging centers, orthopedic practices, hospitals, and clinics).

**Description:** A 2K detector is ideal for lower-volume use in offices. A 4K detector is convenient for higher-resolution imaging in high-volume imaging centers.

**Purpose:** The Vidar system is used in general radiology and orthopedic diagnostic procedures.

**Benefit:** The system offers superior image quality, rapid image acquisition, improved productivity, and ease of use in all digital radiographic examinations. The cost is comparable to that of computed radiography systems. Digital radiography systems improve efficiency by eliminating the costs of staff time associated with film and film processing with conventional x-ray machines and handling cassettes with computed radiology modalities. Patient satisfaction is improved because of shorter examination times, and revenue is enhanced because more examinations can be conducted in each room.

Unlike computed radiology systems, which take two to five minutes for each image to display, the Vidar system displays images in 10 seconds or less.


**Recalled Devices**

**January 31, 2006:** Boston Scientific and the FDA have alerted health care professionals of a class I recall of the Flextome Cutting Balloon system, which is used to open blocked arteries or blood vessels. If the catheter shaft (which places the balloon in the artery) separates while the device is being withdrawn from the patient, the procedure may be prolonged and more in-depth surgery may be required to remove the broken-off piece from the artery.

**Source:** [www.fda.gov/medwatch/safety/2006/safety06.htm#Infusion](http://www.fda.gov/medwatch/safety/2006/safety06.htm#Infusion)

**February 2, 2006:** Baxter Healthcare and the FDA have announced a class 1 recall of all models of Colleague Volumetric Infusion Pumps. These pumps deliver controlled amounts of medications or other fluids through IV, intra-arterial, epidural, or other direct lines into the bloodstream. Reasons for the recall included battery undercharging, false alarms, shutdowns, gearbox wear, under-infusion, and an inability to detect upstream occlusion. Any of these failures may delay or interrupt therapy; this can be life-threatening to patients.

**Source:** [www.fda.gov/medwatch/safety/2006/safety06.htm#Infusion](http://www.fda.gov/medwatch/safety/2006/safety06.htm#Infusion)