**NEW DRUGS**

**Arformoterol Solution for Obstructive Lung Disease**

Sepracor, Inc., has announced the Food and Drug Administration’s (FDA’s) approval of its New Drug Application (NDA) for arformoterol tartrate (Brovana) Inhalation Solution 15 mcg as a long-term, twice-daily maintenance treatment of bronchoconstriction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Brovana is the first long-acting beta$_2$ agonist to be approved as an inhalation solution for use with a nebulizer.

Sepracor completed more than 100 preclinical and 16 clinical studies involving more than 2,000 patients.

For more information on arformoterol, see this month’s Pharmaceutical Approval Update column on page 683.

(Source: Sepracor, October 6, 2006; www.sepracor.com.)

**Glucose Control with Sitagliptin Phosphate**

Sitagliptin phosphate (Januvia, Merck), the first diabetes treatment approved in a new class of drugs known as DDP-4 inhibitors, enhances the body’s own ability to lower elevated blood glucose levels.

The FDA approved the tablets for use in addition to diet and exercise to improve blood sugar levels in patients with type-2 diabetes; the drug can be used alone or in combination with two other oral diabetes medications: metformin (Glucophage, Bristol-Myers Squibb) or a peroxisome proliferator-activated receptor gamma (PPAR) agonist when either of these drugs alone do not provide adequate blood glucose control.

Januvia decreases the amount of sugar made by the body. It is unlikely to cause hypoglycemia because it does not work when blood glucose levels are low. It prolongs the activity of proteins that increase the release of insulin after blood glucose levels rise, such as after a meal. It blocks an enzyme (dipeptidyl peptidase IV or DPP-IV), which breaks down these proteins, leading to better blood sugar control.

Januvia was evaluated in 2,719 patients, but it has not been studied in children under 18 years of age or with medications that cause low blood sugar, such as sulfonylureas and insulin.

It should not be used for patients with type-1 diabetes mellitus or diabetic ketoacidosis.

The usual dose is 100 mg daily. Renally impaired patients may need a reduction in dose to either 50 mg or 25 mg.

(Sources FDA, October 17, 2006; www.glucagon.com/mk-0431.htm.)

**Vorinostat for Skin Cancer**

Vorinostat capsules (Zolinza, Panthenol/Merck) capsules have been approved for the treatment of cutaneous T-cell lymphoma.

The product was approved as part of the FDA’s orphan drug program. Every year in the U.S., this form of lymphoma strikes about three in every one million people, mostly men with an average age of 50 years.

Evidence of the product’s safety and effectiveness was developed in two trials. A response, defined by improved scores on a scale that evaluates skin lesions, occurred in 30% of patients who received the drug, and the response lasted for an average of 168 days.

Serious ADEs included pulmonary embolism, dehydration, deep vein thrombosis, and anemia.

Vorinostat has not been studied in pregnant women, but animal studies suggest that it may cause fetal harm when administered during pregnancy.

(Source: FDA, October 6, 2006.)

**New Flu Vaccine**

The FDA has approved an influenza vaccine (FluLaval, GlaxoSmithKline) for the active immunization of patients 18 years of age and older against influenza virus subtypes A and B. This approval is a major step toward increasing the influenza vaccine supply in the U.S., following the introduction of GSK’s Fluarix before last year’s flu season.

The company added FluLaval to its portfolio of flu products when it acquired the Canadian vaccine manufacturer ID Biomedical Corporation in 2005. FluLaval was granted fast-track review status by the FDA in July 2005. It is marketed under the name Fluviral in Canada.

FluLaval contains noninfectious killed viruses, and it cannot cause influenza. It will be available in 10-dose multidose vials. It is not indicated for use in children or for anyone with known systemic hypersensitivity reactions to egg proteins (in eggs or egg products), chicken proteins, or any component of FluLaval.

(Sources: FDA, October 17, 2006; www.glucagon.com/mk-0431.htm.)

**Posaconazole for Candidal Infections**

Posaconazole oral suspension (Noxafil, Schering-Plough) is now approved for patients with oropharyngeal candidiasis, including infections refractory to itraconazole and/or fluconazole. The Pharmaceutical Approval Update column features posaconazole on page 683.

(Source: Schering-Plough, October 23, 2006.)

**Hepatitis B and Telbivudine**

The FDA has approved telbivudine (Tyzeka, Novartis Pharma Stein AG, Stein) for the treatment of adults with chronic hepatitis B, a viral infection of the liver. HBV can cause lifelong infection; cirrhosis; and eventually liver cancer, liver failure, and death.
Telbivudine contains an active substance that has not been previously approved for marketing in any form in the U.S. The drug was studied in a year-long international clinical trial of 1,367 patients with chronic HBV.

(Source: FDA, October 25, 2006.)

NEW INDICATIONS

Hylan for Ankle and Shoulder Osteoarthritis in Europe

Genzyme Corporation has received European approval to expand the CE Mark labeling for hylan G-F 20 (Synvisc) to include the treatment of pain resulting from osteoarthritis (OA) of the ankle and shoulder. The CE Mark is mandatory for 70% of the products sold in Europe.

Synvisc is sold in more than 60 countries and is approved in the U.S. to treat pain resulting from OA of the knee. The approval of the new indication was based on prospective, multicenter, open investigations in Europe. Treatment with one or two injections was well tolerated.

As a nonsystemic treatment, Synvisc helps avoid some of the side effects associated with some nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors.

Genzyme is pursuing a label expansion in the U.S. that would include an indication for the hip.

(Sources: Genzyme, October 2, 2006; www.ce-marking.org.)

Factor VIIa (Recombinant) For Acquired Hemophilia

Coagulation factor VIIa (recombinant) (NovoSeven, Novo Nordisk) is the first recombinant therapy to be approved for the treatment of bleeding episodes and for the prevention of bleeding in patients with acquired hemophilia who are undergoing invasive surgical procedures.

First introduced in 1999, NovoSeven is currently indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII or factor IX and for bleeding episodes in patients with congenital factor VII deficiency. It is also indicated for prevention of bleeding in surgical interventions or invasive procedures in these patients.

Functionally indistinguishable from naturally occurring activated factor VII, NovoSeven is produced in baby hamster kidney cells that have been genetically engineered to express recombinant factor VII. This agent is not derived from plasma, and it poses no risk of human viral transmission through its use.

(Source: Novo Nordisk, October 17, 2006, www.novoseven-us.com.)

Infliximab Maintains Remission in Ulcerative Colitis

Centocor has announced the FDA’s approval of infliximab (Remicade) for maintaining clinical remission and mucosal healing in patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.

The approval was based primarily on one-year data from the ACT 1 randomized, double-blind, multicenter, placebo-controlled clinical trial. Patients receiving infliximab were nearly three times as likely as patients in the placebo group to maintain clinical remission from their symptoms after one year. In addition, 45% of the infliximab patients, but only 18% of the placebo patients, experienced mucosal healing at week 54.

Infliximab was first approved in the U.S. for the treatment of Crohn’s disease (CD) in 1998. It was later approved for patients with ulcerative colitis in 2005. With this expanded indication for maintenance therapy in ulcerative colitis, infliximab is the only biological agent indicated for inducing and maintaining clinical remission of both types of inflammatory bowel disease.

(Source: Centocor, October 19, 2006.)

Docetaxel Combination For Head and Neck Cancer

Following a priority review of a supplemental new drug application, the FDA has approved docetaxel (Taxotere Injection Concentrate, Sanofi-Aventis) in combination with cisplatin and fluorouracil for the induction treatment of patients with inoperable locally advanced squamous cell carcinoma of the head and neck.

This approval marks the 10th indication for Taxotere (the seventh in the U.S.).

Head and neck cancer usually begins in the cells that line the mucosal surfaces in the mouth, nose, and throat. The term “head and neck” encompasses the oral cavity, salivary glands, paranasal sinuses, nasal cavity, pharynx, larynx, and lymph nodes in the upper part of the neck.

This approval marks the 10th indication for Taxotere (the seventh in the U.S.).

Two More Uses for Rituximab

The FDA has approved two additional uses for rituximab (Rituxan, Genentech/Biogen Idec) for patients with CD20-positive, B-cell non-Hodgkin’s lymphoma (NHL): as a first-line treatment of previously untreated patients with follicular NHL in combination with cyclophosphamide, vincristine, and prednisolone (CVP) chemotherapy, and as a treatment for low-grade NHL in patients with stable disease or who have achieved a partial or complete response following first-line treatment with CVP chemotherapy.

A therapeutic antibody, rituximab depletes CD20-positive B-cells without targeting stem cells or existing plasma cells.

In 1997, rituximab was approved to treat relapsed or refractory low-grade or follicular, CD20-positive, B-cell NHL. In 2006, it was approved for treating diffuse large B-cell lymphoma (DLBCL) in combination with cyclophosphamide, dox-
Bevacizumab Combination In Non-Small Cell Lung Cancer

The FDA has approved bevacizumab (Avastin, Genentech) for use in combination with carboplatin and paclitaxel chemotherapy for the first-line treatment of patients with unresectable, locally advanced, recurrent or metastatic nonsquamous, non–small cell lung cancer, the most common type of lung cancer.

In a phase 3 study, bevacizumab plus chemotherapy resulted in a 25% improvement in overall survival, compared with chemotherapy alone.

In 2004, the FDA approved the drug for the first-line or second-line treatment of metastatic colon or rectal carcinoma in combination with IV 5-fluorouracil-based chemotherapy.

Genentech plans to initiate a program in January 2007 to cap the overall expense of bevacizumab to $55,000 per year for each eligible patient with any FDA-approved indication, whether or not the patients are insured.

(Source: Genentech, October 11, 2006.)

Risperidone Helps Reduce Autistic Behaviors

Risperidone (Risperdal, Janssen) orally disintegrating tablets are now indicated for the symptomatic treatment of irritability in autistic children and adolescents.

The approval is the first for the use of a drug to treat behaviors associated with autism in children, such as irritability, aggression, deliberate self-injury, and temper tantrums.

Risperidone has been approved since 1993 for the short-term treatment of adults with schizophrenia and since 2003 for the short-term treatment of adults with acute manic or mixed episodes associated with extreme mood swings.

The product’s effectiveness in the symptomatic treatment of irritability associated with pediatric autistic disorders was established in two eight-week, placebo-controlled trials in 156 patients five to 16 years of age.

(Source: FDA, October 6, 2006.)

Donepezil for Severe Alzheimer’s Dementia

The FDA has approved donepezil HCl (Aricept, Eisai) for treating severe dementia in patients with Alzheimer’s disease (AD).

Donepezil was previously approved to treat mild-to-moderate dementia of the Alzheimer’s type. It now becomes the first product approved for the treatment of all degrees of severity of the disease.

The approval is based on two new clinical studies conducted in Sweden and Japan in more than 500 patients with severe AD. The effectiveness of therapy with donepezil was determined by evaluating cognitive skills (memory, language, orientation, and attention) and overall functioning. Patients receiving donepezil performed better in both measures than patients receiving placebo.

(Source: FDA, October 16, 2006.)

Imatinib Benefits Five Rare Disorders

Imatinib mesylate tablets (Gleevec, Novartis) have been approved for patients with five distinct and potentially life-threatening disorders. This approval represents the first time that a regulatory authority has simultaneously approved one drug for this many disorders.

Imatinib is now indicated for seven diseases, including two solid tumors and five blood disorders with molecular targets known to be inhibited by the drug. The new approval covers one solid tumor (dermatofibrosarcoma protubersans) and four rare blood disorders (relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), certain forms of myelodysplastic/myeloproliferative diseases, hypereosinophilic syndrome/chronic eosinophilic leukemia, and aggressive systemic mastocytosis).

Imatinib targets the activity of tyrosine kinases, which may play important roles within some cancer cells, including platelet-derived growth factor receptor.

(Source: Novartis, October 19, 2006.)
NEW FORMULATIONS

Ciclesonide Nasal Spray
For Allergic Rhinitis

The FDA has approved ciclesonide nasal spray (Omnaris, Altana Pharma), a corticosteroid for treating nasal symptoms associated with seasonal and perennial allergic rhinitis (hay fever) in adults and in children 12 years of age and older.

The precise mechanism of action is unknown, although corticosteroids suppress the immune response.

The safety and efficacy of the product were studied in four randomized, placebo-controlled clinical trials ranging in duration from two weeks to a year. Patients receiving the spray had an 8% to 10% greater reduction in nasal symptoms compared with subjects taking placebo.

Ciclesonide, under the trade name Alvesco, is also used in an inhaler in a liquid formulation for patients with asthma.

(Source: FDA, October 23, 2006.)

Atazanavir Sulfate Combo
For HIV-1 Infection

A new 300-mg single capsule formulation of atazanavir sulfate (Reyataz, Bristol-Myers Squibb) has been approved for adults with HIV-1 infection as part of combination therapy.

Taken once daily along with ritonavir (Novir, Abbott) and food as part of an anti-HIV drug regimen, the capsule formulation can replace two atazanavir 150-mg capsules for patients who have previously received anti-HIV medications, for those who will be receiving tenofovir disoproxil fumarate (Viread, Gilead), and for those who have never taken anti-HIV drugs that require efavirenz (Sustiva, Bristol-Myers Squibb) as part of their anti-HIV drug regimen.

The FDA initially approved atazanavir in 2003. Abbott will continue to produce the 200-mg, 150-mg, and 100-mg once-daily capsules.

(Source: Bristol-Myers Squibb, October 20, 2006.)

DRUG NEWS

Atypical Antipsychotic Agents
For Alzheimer’s Disease:
Risks May Outweigh Benefits

Atypical antipsychotic drugs are now common choices for treating delusions, hallucinations, aggression, and agitation in patients with Alzheimer’s disease (AD). These drugs are considered to be at least as effective as haloperidol decanoate (Haldol, Ortho-McNeil) and other conventional antipsychotic agents, with a lower risk of most adverse effects. However, studies have been relatively sparse and data have been inconsistent, say members of the Clinical Antipsychotic Trials of Intervention Effectiveness Alzheimer’s Disease Study Group. Their own findings suggest that the adverse effects of atypical antipsychotics offset the advantages in patients with AD.

In a multicenter, double-blind, placebo-controlled trial, 421 outpatients with AD and psychosis, aggression, or agitation were randomly assigned to receive olanzapine (Zyprexa, Eli Lilly) (mean, 5.5 mg/day), quetiapine fumarate (Seroquel, AstraZeneca) (mean, 56.5 mg/day), risperidone (Risperdal, Janssen) (mean, 56.5 mg/day), quetiapine fumarate (Seroquel, AstraZeneca) (mean, 56.5 mg/day), risperidone (Risperdal, Janssen) (mean, 1 mg/day), or placebo. Doses were adjusted as needed, and patients were followed for up to 36 weeks. Risperidone and olanzapine doses were within the recommended ranges, and the quetiapine dose was one-half to one-quarter of that used in two nursing-home trials.

By 12 weeks, improvement was seen in 32% of patients receiving olanzapine, in 29% of those receiving risperidone, 26% of those taking quetiapine, and 21% of those receiving placebo. However, 77% to 85% of patients discontinued treatment. Overall, 24% of the olanzapine patients, 18% of the risperidone patients, 16% of the quetiapine patients, and 5% of the placebo patients withdrew from treatment because of adverse events or intolerability.

Sedation was very probable with olanzapine, which was also associated with increased confusion. Extrapyramidal signs and symptoms with both risperidone and olanzapine were common reasons for stopping treatment.

Patients gained weight with olanzapine and risperidone and lost weight with placebo. The possibility that antipsychotic drugs might cause metabolic syndrome in the elderly requires further investigation, the researchers advise.


Ezetimibe/Simvastatin
Label Revision

The product label for ezetimibe/simvastatin (Vytorin, Merck/Schering-Plough) may now show that it was more effective than rosuvastatin calcium (Crestor, AstraZeneca) in lowering low-density lipoprotein-cholesterol levels at all doses that were compared. In a study of 2,959 patients, high cholesterol levels were reduced by 52% to 61% with Vytorin 10/20 to 10/80 mg and by 46% to 57% with Crestor 10 to 40 mg. Both drugs raised high-density lipoprotein-cholesterol by 8%.

(Source: Merck/Schering-Plough, October 6, 2006.)

NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: Prodisc-L
Manufacturer: Synthes Spine, Inc., West Chester, PA
Approval Date: August 14, 2006
Use Classification: This artificial intervertebral disc is used for spinal arthroplasty in skeletally mature patients with degenerative disc disease at a single level from L3-S1.
Description: The weight-bearing
A modular implant consists of two cobalt-chromium alloy endplates available in two lordotic angles (6 degrees and 11 degrees) and a polyethylene inlay (10, 12, or 14 mm in thickness). Both endplates are plasma-sprayed with commercially pure titanium. Fixation is intended through bony ingrowth, with initial stabilization by a large central keel and two small spikes on the endplate surface.

The inlay snap-locks into the inferior endplate and provides a convex-bearing surface to articulate with the concave-bearing surface of the superior endplate. Range of motion is 13 degrees of flexion, 7 degrees of extension, ±10 degrees of lateral bearing, and ±3 degrees of axial rotation.

**Purpose:** The device is indicated for patients who have no more than grade 1 spondylolisthesis and who have not responded successfully to at least six months of conservative treatment.

**Benefits:** In clinical studies, disc recipients maintained or improved range of motion, experienced pain relief sooner, recovered more quickly, and were more satisfied with the procedure at two years than patients treated by circumferential fusion. The disc resulted in decreased surgical time and in a shorter hospital stay.

**Precautions:** Contraindications include active systemic infection, infection localized to the implant site, osteopenia or osteoporosis, bony lumbar spinal stenosis, allergy or sensitivity to implant materials, isolated radicular compression symptoms, pars defect, an involved vertebral endplate of less than 34.5 mm in thickness, or 34.5 mm in thickness, and repeated intervention, compared with bare-metal stents, with no corresponding increase in death, cardiac death, or heart attacks. Boston Scientific is conducting additional studies to evaluate the stent in an even broader range of patients and for various lesions.

**Purpose:** The FDA released a statement on coronary drug-eluting stents. Boston Scientific’s Taxus stent is indicated for improving luminal diameter. A large body of clinical evidence, including randomized, controlled trials in nearly 3,500 patients, showed that the Taxus drug-eluting stent substantially reduced the risk of restenosis and repeated intervention, compared with bare-metal stents, with no corresponding increase in death, cardiac death, or heart attacks. Boston Scientific is conducting additional studies to evaluate the stent in an even broader range of patients and for various lesions.

**Name:** NaviStar ThermoCool Irrigated Deflectable Catheter

**Manufacturer:** Biosense Webster, Inc. (J&J), Diamond Bar, CA

**Approval Date:** August 11, 2006

**Use Classification:** This diagnostic/ablation tip catheter is used to destroy (ablate) heart tissue that is causing an abnormal heartbeat. The catheter is used with a radiofrequency generator to treat recurrent, sustained monomorphic ventricular tachycardia that has not responded to drugs or medical devices because of previous myocardial infarction.

**Description:** When used with the Carto EP/XP Navigation System, the device provides location information, and it can be used for catheter-based cardiac electrophysiological mapping (stimulation and recording). The catheters are available in B, C, D, F, and J curves. Except for the J-curve type (available with a thermocouple only), all of the catheters are equipped with either a thermistor or thermocouple for temperature sensing.

**Purpose:** Watching a screen, the doctor places the ablation catheter in the exact spot to treat the abnormally rapid heartbeat. After the catheter is in place, the doctor turns on the energy from the generator to heat the tip of the catheter. This heat destroys a small part of the heart that is causing the abnormal beat.

**Benefit:** Ablating a small amount of heart tissue blocks the abnormal electrical pathways in the heart that cause the ventricular tachycardia.

**Sources:** www.medscape.com; www.fda.gov

**Name:** Cryopreserved OrCel

**Manufacturer:** Ortec International, Inc./Cambrex Bio Science Walkersville, Inc., Walkersville MD

**Approval Date:** September 29, 2006

**Use Classification:** Cryopreserved (frozen) OrCel is indicated for patients with epidermolysis bullosa who have recessive dystrophic epidermolysis bullosa and who are undergoing hand reconstruction. Epidermolysis bullosa is a congenital skin disorder characterized by painful ulcerations and scarring, resulting in deformity of the hands and feet. The device is also used to cover donor sites created during the surgery. Repeated surgical procedures are usually required to replace the skin.

**Description:** OrCel is composed of a collagen sponge seeded with allogeneic epidermal and dermal cells, which secrete growth factors and cytokines normally found in adult human wounds. The cells appear to promote tissue repair.

**Purpose:** The FDA gave OrCel an approvable Humanitarian Device Exemption. This is similar to a pre-market approval application but is exempt from certain effectiveness requirements of the Medical Device Act. This clearance allows medical devices that provide safe treatment to be available for patients with rare medical conditions.

**Benefit:** The product is helpful for patients who need skin replacement.

**Sources:** www.pharmacyonesource.com; www.biospace.com

**News Update: Taxus Cardiac Stent**

On September 14, 2006, the FDA released a statement on coronary drug-eluting stents. Boston Scientific’s Taxus stent is indicated for improving luminal diameter. A large body of clinical evidence, including randomized, controlled trials in nearly 3,500 patients, showed that the Taxus drug-eluting stent substantially reduced the risk of restenosis and repeated intervention, compared with bare-metal stents, with no corresponding increase in death, cardiac death, or heart attacks. Boston Scientific is conducting additional studies to evaluate the stent in an even broader range of patients and for various lesions.

**Sources:** www.therapeuticsdaily.com; www.fda.gov)