NEW DRUGS

ADHD Drug May Offer Less Potential for Abuse

The Food and Drug Administration (FDA) has approved lisdexamfetamine dimesylate (Vyvanse, Shire plc/New River Pharmaceuticals) for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

This prodrug is therapeutically inactive until it is metabolized in the body. When it was given orally and intravenously in two studies, it produced fewer subjective responses on a scale of “drug-liking effects,” compared with d-amphetamin at equivalent doses.

The FDA proposes that Vyvanse be classified as a Schedule II controlled substance. This medication is designed to provide a lower potential for abuse.


NEW INDICATIONS

Antihemophilic Factor For von Willebrand’s Disease

Antihemophilic factor/von Willebrand factor complex (human) (Alphanate, Grifols) has been approved for the treatment of congenital von Willebrand’s disease (vWD) in connection with surgery or other invasive procedures. Alphanate is approved for the treatment of vWD, and it has also been used to treat hemophilia A for more than a decade.

An inherited bleeding disorder, vWD is caused by a defect or deficiency of a blood-clotting protein (von Willebrand factor). This factor is needed in the initial stages of blood clotting, vWD affects 1% to 2% of the population.

(Source: Grifols, February 2, 2007.)

Adalimumab for Crohn’s Disease

The FDA has approved adalimumab (Humira, Abbott) to treat adults with moderately to severely active Crohn’s disease, a chronic inflammatory disease of the intestines. This monoclonal antibody helps to reduce excessive levels of human tumor necrosis factor–alpha, which plays a role in abnormal inflammatory and immune responses.

The labeling includes a boxed warning about potential serious adverse events, including tuberculosis, opportunistic infections, and sepsis.

Adalimumab was previously approved for the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

For more information on adalimumab, see Meeting Highlights, page 160.

(Source: FDA, February 27, 2007.)

Duloxetine for Generalized Anxiety Disorder

Eli Lilly has announced the FDA’s approval of the antidepressant duloxetine HCl (Cymbalta) in patients with Generalized Anxiety Disorder (GAD). GAD affects more than 6.5 million American adults each year.

In three randomized, double-blind, placebo-controlled studies of more than 800 non-depressed adults with GAD, the drug significantly improved core anxiety symptoms, compared with placebo. Treated patients reported an improved ability to perform everyday activities.

Duloxetine is also approved for adults with Major Depressive Disorder and diabetic peripheral neuropathic pain.

(Source: Eli Lilly, February 26, 2007.)

Drospirenone/Ethinyl: A Contraceptive To Relieve Acne

Berlex, Inc., a U.S. affiliate of Bayer Schering Pharma in Germany, has announced a new indication for 3 mg drospirenone/20 mcg ethinyl estradiol (Yaz) to treat moderate acne vulgaris in women who desire an oral contraceptive.

Yaz was approved as an oral contraceptive in March 2006 and as a treatment for the emotional and physical symptoms of premenstrual dysphoric disorder.

This product has shown efficacy in treating premenstrual irritability, moodiness, anxiety, bloating, and increased appetite that are severe enough to affect a woman’s activities, work, or relationships.

Unlike other progestins, drospirenone has a mild diuretic effect and can block male sex hormones that can cause acne. Acne tends to flare up in women just before or during menstruation.

Investigator ratings of “clear” and “almost clear” skin were nearly four times greater in the treated patients than in those receiving placebo.

Most of the women tolerated treatment well. Adverse effects included upper respiratory tract infections, irregular bleeding, headache, nausea, sinusi-
DRUG NEWS

Final Approval for Sunitinib In Advanced Kidney Cancer

New labeling for sunitinib malate (Sutent, Pfizer) now includes the first-line treatment of advanced renal cell carcinoma.

This agent was originally approved in January 2004 for the treatment of advanced kidney cancer under an accelerated approval. With the new labeling, the accelerated approval has now been converted to regular approval.

Sunitinib is also indicated for patients with gastrointestinal stromal tumors after disease progression with, or intolerance to, imatinib mesylate (Gleevec, Novartis). This agent, which is indicated for the treatment of myelodysplastic syndromes (MDS), may now be used in a clinic or hospital setting.

On May 19, 2004, azacitidine became approved by the FDA for the treatment of advanced renal cell carcinoma.

Because this medication is associated with neutropenia and thrombocytopenia, complete blood counts should be performed as needed to monitor responses and toxicity. Caution is needed for patients with impaired renal function.

Women should not breast-feed while taking azacitidine.

(Source: Berlex, January 29, 2007.)

NEW FORMULATION

IV Route for Azacitidine In Myelodysplastic Syndromes

The FDA has approved a New Drug Application (NDA) supplement to add intravenous (IV) use as a new route of administration for azacitidine (Vidaza, Pharmion). This agent, which is indicated for the treatment of myelodysplastic syndromes (MDS), may now be infused over a period of 10 to 40 minutes in a clinic or hospital setting.

IV dosing remains the same as in the previous subcutaneous formulation, 75 mg/m² daily for seven days every four weeks.

On May 19, 2004, azacitidine became the first drug approved by the FDA for MDS.

Because this medication is associated with neutropenia and thrombocytopenia, complete blood counts should be performed as needed to monitor responses and toxicity.

Caution is needed for patients with impaired renal function.

Women should not breast-feed while taking azacitidine.

(Source: Pharmion, January 29, 2007.)

DRUG NEWS

Label Changes for Antibiotic Telithromycin

The FDA has announced revisions to the labeling for the antibiotic telithromycin (Ketek, Sanofi-Aventis).

Two of the three previously approved indications are being removed from the drug’s label: acute bacterial sinusitis and acute bacterial exacerbations of chronic bronchitis. The agency has determined that the balance of benefits and risks no longer supports approval of the drug for these indications.

Originally approved in 2004, telithromycin will remain on the market for the treatment of mild-to moderate community-acquired pneumonia.

A boxed warning is being added to state a contraindication for patients with myasthenia gravis. Warnings about the potential for hepatic toxicity were strengthened in 2006. A patient guide will be provided with each prescription.

(Sources: N Engl J Med, January 11, 2007; Pfizer, February 17, 2007.)

FDA Alert for Darbepoetin alfa

The FDA has issued an alert about the use of darbepoetin alfa (Aranesp), an erythropoiesis-stimulating agent (ESA), to treat anemia in cancer patients who are not receiving chemotherapy. In a large clinical trial, patients randomly received either the approved dosing regimen of darbepoetin alfa or placebo. The treated patients had a higher death rate and no reduction in the need for transfusions, compared with placebo patients.

ESAs are not approved by the FDA to treat anemia in cancer patients not receiving chemotherapy.

(Source: FDA, February 20, 2007.)

NEW DRUGS

Boxed Warning to Be Added For Asthma Drug Omalizumab

Genentech has been instructed to add a boxed warning to its product label for omalizumab (Xolair), which is used to treat patients with asthma related to allergies.

The warning emphasizes that this medication may cause anaphylaxis. The FDA has also asked Genentech to revise the label and provide a medication guide for patients to strengthen the existing warning for anaphylaxis.

Omalizumab was approved in 2003 to treat adults and adolescents with moderate-to-severe persistent asthma who tested positive for a perennial allergen (pollen, grass, or dust) and whose symptoms were inadequately controlled with inhaled steroids.

(Source: FDA, February 21, 2007.)

New Sirolimus Dosage For Kidney Recipients

The FDA has approved new dosing recommendations for Wyeth’s immunosuppressant drug sirolimus (Rapamune). Sirolimus is indicated to prevent organ rejection in kidney recipients 13 years of age or older.

It is recommended that a sirolimus-based regimen be used in combination with cyclosporine and corticosteroids for the first year following transplantation. Preventing acute rejection is the highest priority during this time.

Patients at high immunological risk tend to experience acute rejection, compared with patients at low-to-moderate risk. African-Americans, patients who have undergone previous transplantation and who have lost a kidney transplant for immunological reasons, as well as patients with high-panel-reactive antibodies are at greater risk. For patients with high-panel reactive antibodies, it is more difficult to find a compatible organ donor.

(Source: FDA, February 21, 2007.)
Eighty-nine percent of African-Americans have a fully functioning kidney one year after transplantation, compared with 91% of white kidney transplant recipients. By five years afterward, the figures are only 60% of African-Americans, compared with 72% of white recipients.

(Sources: Wyeth, February 2, 2007; www.rapamune.com.)

**Warning for Rotavirus Vaccine**

The FDA has notified physicians and parents of potentially life-threatening twisting of the intestines (intussusception) in infants who received Merck’s vaccine, RotaTeq, to protect against a virus that is the leading cause of early childhood diarrhea.

Rotavirus affects millions of children worldwide, mostly in developing countries. In the U.S., the virus is responsible for more than 400,000 doctor’s visits and as many as 60 deaths.

The FDA said that the RotaTeq label would mention the possibility of intussusception.

It is unknown whether the vaccine, approved last year, caused the 28 new cases. Some of the infants needed intestinal surgery. There have been no reports of deaths.

Eight years ago, Wyeth withdrew its own rotavirus vaccine because of similar reports of intestinal blockage. Pediatricians and parents can call 1-800-822-7967 to report any cases of intussusception.

(Sources: Associated Press, February 13, 2007; Philadelphia Inquirer, February 14, 2007.)

**Comparing Adverse Effects in Around-the-Clock and As-Needed Analgesia**

Nausea, vomiting, drowsiness, lack of energy, urinary retention—these are the side effects of analgesic medications that can be enough to derail pain management for cancer patients. A study of 174 patients with bone metastases suggests that around-the-clock (ATC) prescriptions plus as-needed (p.r.n.) drugs and ATC opioids are often responsible for these effects.

A study from the University of California, San Francisco; the University of Nebraska; and the University of Texas Southwestern Medical Center, Dallas, was part of a larger clinical trial that evaluated the effectiveness of the Pro-Self Pain Control Program in 212 patients with cancer.

Four types of analgesic prescriptions were analyzed: no opioids, p.r.n. opioids only, ATC opioids only, or ATC plus p.r.n. opioids. The most common short-acting opioids were acetaminophen/codeine phosphate (Fioricet, Watson) and acetaminophen/hydrocodone bitartrate (Vicodin, Abbott). The most common controlled-release (CR) opioids were morphine and transdermal fentanyl CR (Duragesic, PriCara).

Patients kept diaries on pain management and reported on 11 adverse effects, including difficulty concentrating, lack of energy, nausea, vomiting, and sleep problems. They were asked to rate the number of hours per day and the number of days per week during which pain interfered with their mood or activities and to indicate the amount of relief they received from their pain medication in the previous week. Another scale measured the patients’ ability to perform activities of daily living.

The researchers found no significant differences in “pain now,” average pain, worst pain, or length of time in pain among the four groups. However, total scores from pain interference were significantly higher in patients using ATC plus p.r.n. opioids, compared with those using no opioids. The amount of pain relief was significantly lower in patients receiving no opioids than in those receiving p.r.n. opioids only.

The highest prevalence for the most side effects was found in the ATC-only group and in the ATC plus p.r.n. groups. Despite clinical practice guideline recommendations to treat side effects aggressively, the prevalence rates for most analgesic side effects range from 25% to 80%. The prevalence of all 11 side effects in the two groups ranged between 25% and 83%.

Not surprisingly, a higher opioid dose was a risk factor for many side effects. The dose taken by patients in the ATC plus p.r.n. group was 3.5 times higher than that in the ATC-only group and 17 times higher than that in the p.r.n.–only group.

It is worth noting that the patients tended to rate side effects as mild to moderate, regardless of the prescription. The researchers suggest that the patients might have become tolerant of some of the side effects or were using strategies to overcome them.

(Source: J Pain Symptom Manage 2007;33:67–77.)

**Oral Gabapentin: Headache Relief After Spinal Anesthesia**

Although spinal anesthesia has been performed since the late 1800s, postdural puncture headache (PDPH) continues to be a problem for patients and a challenge for clinical staff members.

The cardinal feature of this type of headache is associated with posture; the pain worsens when patients are sitting or standing and improves when patients are supine. Pain occurs in the frontal, temporal, or occipital regions on both sides and can be accompanied by neck stiffness, backache, and nausea. In approximately 15% of cases, PDPH is so severe that patients cannot eat, drink, or carry out activities of daily living.

Researchers from Kocatepe University in Afyon, Turkey, suggest that oral...
Women with type-2 diabetes who take rosiglitazone (Avandia, Avandamet, or Avandaryl, GlaxoSmithKline) may be more likely to experience bone fractures compared with women who use other agents. The FDA and GlaxoSmithKline have advised physicians to consider fracture risk when they treat women with these agents.

In one study, more than 4,000 patients were randomly assigned to take rosiglitazone, metformin (Glucophage), or glyburide (Diabeta, Micronase) for four to six years. During that time, women taking rosiglitazone were more likely to have bone fractures than women taking either metformin or glyburide. Most of the fractures affected the bones in the upper arm, hand, or foot.

This problem was not seen in men taking rosiglitazone.

In another study of 50 postmenopausal women, those patients taking rosiglitazone had a 1.9% decrease in total hip bone density after 14 weeks of treatment, whereas those taking a placebo experienced a reduction of 0.2%.

It is not clear how the drugs affect fracture risk, but it is thought that the medication decreases bone formation.

(Source: J Clin Endocrinol Metab, January 30, 2007; WebMD Medical News, February 22, 2007; FDA/GlaxoSmithKline, February 2007.)

Should Memantine Be Given Across the Board?

Arbitrarily dividing patients with Alzheimer’s disease (AD) into groups according to disease severity may keep some of them from benefiting from treatment, suggest findings from a meta-analysis study.

Researchers from Baylor College of Medicine, the University of Rochester, the University of South Florida (Tampa), and Forest Laboratories found that memantine (Namenda, Forest), which is usually reserved for patients with severe symptoms, was effective and well tolerated across the spectrum from cases of AD that were mild to severe.

The researchers evaluated six randomized, placebo-controlled trials involving more than 2,300 patients. In most of the studies, the dose was 10 mg twice a day; in one study, the dose was 20 mg once daily.

In general, memantine showed statistically significant benefits in global and functional outcomes, as well as in cognition, in all disease categories. For all levels of severity, the effect of monotherapy on cognition was also statistically significant.

The overall frequency of adverse effects was low, usually much less than 10%, in both the memantine groups (1,242 patients) and the placebo groups (1,069 patients). Somnolence was more likely in the memantine groups, as were constipation, vomiting, hypertension, and abnormal gait, all of which occurred in fewer than 4% of patients.

(Source: Alzheimer Dementia 2007;3:7–17.)

No Need for Heparin After Some Procedures For Myocardial Infarction

Heparin can safely be discontinued from the routine after primary percutaneous coronary intervention (PCI) for acute myocardial infarction (AMI) for some patients, say researchers who conducted the largest investigation to examine the issue.

In the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial, 2,082 patients with AMI who underwent primary PCI were randomly assigned to receive stents or angioplasty, with or without abciximab (ReoPro, Centocor/Eli Lilly). In a subset of 976 patients who did not receive abciximab, researchers compared the outcomes between 758 patients who received postprocedural heparin for a median of two days and those who did not. The patients were followed for 12 months.

Rates of in-hospital death, reinfarction, disabling stroke, and major adverse cardiac events were similar for patients who received postprocedural heparin and for those who did not. In 421 patients who received angioplasty, heparin was associated with a lower incidence of major adverse cardiac events, both in the hospital and at one year. The patients, paradoxically, were also less likely to have moderate or severe bleeding (2.3% vs. 8.9%).

Among the 555 patients who underwent stenting, however, heparin given after the procedure was associated with increased bleeding and hospitalization...
costs without a reduction in early or late major adverse cardiac events.

(Source: Am J Cardiol 2007;99:202–207.)

FDA Orders Patient Guides For ADHD Drugs

The FDA has directed the makers of all drug products approved for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) to develop patient-medication guides to alert patients to possible associated cardiovascular risks and risks of adverse psychiatric symptoms and to advise them of precautions.

The handouts are given to patients, families, and caregivers when a drug is dispensed. Patients using ADHD products should read the information before taking the medication and should talk to their doctors if they have any concerns.

The new guides reflect changes ordered last May in the warnings section of the physician labeling.

From 1993 to February 2005, the FDA received 27 reports of unexpected death in patients under 18 years of age who had taken one of the medications. It is not clear whether the deaths resulted from the ADHD drugs or from underlying cardiovascular problems.

The following drugs are the focus of the revised labeling and new patient guides: Adderall, Concerta, Daytrana Transdermal System, Desoxyn, Dexedrine Spansule, Focalin, Metadate CD, Methylan oral solution and chewables, Ritalin, and Strattera.

(Source: FDA, February 21, 2007.)

NEW MEDICAL DEVICES

Marvin M. Goldenberg, PhD, RPh, MS

Name: Olympic Cool-Cap

Manufacturer: Olympic Medical Corp., a Natus company, San Carlos, CA; Seattle, WA

Approval Date: December 20, 2006

Use Classification: The cap is indicated for term infants born with moderate-to-severe hypoxic–ischemic encephalopathy (HIE), a potentially fatal brain injury caused by low levels of oxygen.

Description: The fitted cap covers the infant’s head and maintains a steady flow of water at a selected cool temperature. In a study of 234 infants, the cap was found to be safe and effective. At 18 months of age, there were fewer deaths and fewer severe cases of neurodevelopmental disability in the cooled group compared with the control group.

Purpose: The cap is designed to prevent or reduce brain damage by keeping the infant’s head cool while the body is maintained at a slightly below-normal temperature.

Benefit: The cap provides a hopeful outcome for 5,000 to 9,000 babies each year who are born in the U. S. with HIE. Before this device was approved, there had been no effective therapy for HIE other than supportive care. Up to 20% of these patients died, and 25% experienced permanent disability because of neurological deficits.

Precautions: The device should not be used if the infant weighs less than 1,800 g at birth, if there is evidence of head trauma or skull fracture that is causative or intracranial bleeding, or if the infant has an imperforate anus.

Source: www.fda.gov/cdrh/mda/docs/P040025

Name: Visumax Femtosecond Laser System

Manufacturer: Carl Zeiss Meditec, Inc., Dublin, CA

Approval Date: January 18, 2007

Use Classification: The laser system is designed to provide smooth and precise flap-cutting capabilities for refractive ocular surgery.

Description: Using a unique pivoting patient bed and an integrated data management system, surgeons can complete refractive procedures without the need to move the patient and without performing redundant data entries. Either platform may be used separately or in conjunction with other laser systems but without the full system integration benefits.

Purpose: This technology, combined with the Zeiss MEL 80 excimer laser, delivers excellent outcomes, increases the potential for an optimized workflow for surgeons, and provides improved comfort for patients.

Benefit: In the field of refractive surgery, the apparent benefits of the system are not limited to those normally recognized for a femtosecond laser flap because of the special design of the contact glass and the low increase in intraocular pressure. Perfusion of the central retinal artery is not impaired, and patients are able to see the fixation light throughout the procedure. The system also offers a new level of cutting accuracy for corneal incisions.

Excellent visual acuity was achieved, with results of up to 20/10 one day postoperatively; vision in 93% of patients was corrected to 20/20 or better, with 41% achieving 20/12.5 or better at six months. There were no instances of transient light sensitivity syndrome or diffuse lamellar keratitis in any of the treated patients.


Stent Controversy and Recommendations

In December 2006, the FDA’s Circulatory System Devices Panel heard two days of testimony from physician researchers, advocacy groups, and two manufacturers as members sought to answer the safety question posed by recent reports of increased risk for stent thrombosis with drug-eluting stents. The
panel recommended that physicians remain cautious about off-label use and that patients continue taking clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi-Aventis) for up to one year.

There appears to be a risk for adverse outcomes for these stents, but it is not clear that the risk factors are any worse than those for bare-metal stents. A recent article stated that the extended use of clopidogrel in patients with drug-eluting stents might be associated with a reduced risk for death or myocardial infarction. However, the appropriate duration of clopidogrel administration can be determined only within the context of a large-scale, randomized clinical trial.

After the meeting, the FDA stated that drug-coated coronary stents remained safe and effective for patients with clinical and coronary anatomic features similar to those treated in the pivotal trials that had been conducted for FDA approval.

Although stent thrombosis occurs at low rates, the new data raise important questions. However, not enough information is available to draw conclusions about, for example, what causes thrombosis in patients with these stents, how often the problem occurs, the circumstances under which it occurs, or what the risk factors are in a given patient.

On January 12, 2007, the Society for Cardiovascular Angiography and Interventions advised physicians on practical steps for reducing the risk of a rare but serious complication associated with the use of drug-eluting stents. The decision whether to treat a patient with such a stent—rather than a bare-metal stent or bypass surgery—must be made on a case-by-case basis, and physicians must consider the relative risks and benefits of each therapy. This determination will vary according to each patient’s medical history, coexisting illnesses, and lesion characteristics.

Patients must be carefully evaluated for their ability to adhere to long-term therapy with dual anticlotting medications. Physicians must pay careful attention to stent implantation techniques, including intravascular ultrasound; screening for arterial calcifications; and pretreatment of complex lesions.

Patients should take dual anticlotting medications for at least three to six months, preferably for 12 months, unless there is a high risk of bleeding. In patients with a higher-than-average risk for late stent thrombosis (e.g., in diabetic patients), physicians should consider continuing dual anticlotting drugs for longer than 12 months as well as testing patients’ responsiveness to these drugs and adjusting dosages as needed.

Therapy should be stopped only after careful consideration of each patient’s situation.

Sources: JAMA 2007;297:159–168; www.todayincardiology.com; www.pharmalive.com

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