First Generic Bupropion Hydrochloride Extended-Release Tablets Approved

On December 15, 2006, the Food and Drug Administration (FDA) approved the first generic version of Wellbutrin XL® (Bupropion hydrochloride) Extended-Release Tablets indicated for the treatment of major depressive disorder (MDD). In 2005, Wellbutrin XL® was the twenty-first highest selling brand name drug in the United States so this approval should bring significant savings to many Americans being treated for depression. Bupropion hydrochloride Extended-Release Tablets are manufactured by Anchen Pharmaceuticals Inc. Teva will sell the product within Anchen’s 180-day exclusivity and has already commercially shipped its 300 mg generic version of Wellbutrin XL®.

New Combination Topical Product Approved for Treatment of Acne

On November 7, 2006, the FDA approved Ziana™, a combination of clindamycin, a lincosamide antibiotic, and tretinoin, a retinoid, for topical treatment of acne vulgaris in patients twelve years of age and older. The product is indicated for application, in a pea-sized amount, once daily at bedtime. The most frequent reactions to the product include skin erythema, scaling, itching, burning, and stinging. Other adverse effects are nasopharyngitis, pharyngolaryngeal pain, dry skin, cough, and sinusitis. The product, manufactured by Medicis, is currently available.

Pipeline Agent: Rimonabant by Sanofi-Aventis for Weight Management

In the United States, as determined in 2005, approximately 60.5 percent of the adult population is overweight and approximately 23.9 percent are obese. As much as ten percent of an industrialized nation’s healthcare budget can be spent on obesity and related comorbidities. A novel cannabinoid (CB1) receptor antagonist, rimonabant, is approved in Europe as an adjunct to diet and exercise for treatment of obese patients or patients who are overweight with associated risk factors (type 2 diabetes and dyslipidemia). A particular observation of cannabis smokers often having hunger pangs led to the development of strategies to block the cannabinoid receptor pathway. CB1 receptors are located in areas of the brain responsible for appetite regulation as well as in several tissues/organs, including adipose tissue, the gastrointestinal tract, liver, skeletal muscle and autonomic nervous system.

In February, 2006, the FDA issued an approvable letter for rimonabant for weight management. A nonapprovable letter was issued for smoking cessation. In clinical trials, a potential role for rimonabant in cardiovascular disease and type 2 diabetes has also been demonstrated. Sanofi-Aventis continues to work with the FDA to resolve issues required for approval of rimonabant for both weight management and smoking cessation.

Rimonabant is to be available as a 20 mg tablet to be taken once daily before breakfast. Its safety and efficacy have not been evaluated for periods longer than two years. In the fasting state, multiple once-daily doses of 20 mg in healthy subjects achieved maximum plasma concentrations in approximately two hours and steady state plasma levels within thirteen days. Peripheral volume of distribution seems to be related to body weight with obese patients having a higher volume of distribution and taking longer to reach steady state. In vitro, rimonabant demonstrates high human plasma protein binding. Approximately three percent of the dose is eliminated in the urine and approximately eighty-six percent of the dose is excreted in the feces as unchanged drug and metabolites. The drug is metabolized primarily by the liver including the CYP3A enzyme system and its metabolites are inactive. The elimination half-life of the drug is longer (sixteen days versus nine days) in obese patients versus non-obese patients due to a larger volume of distribution. Mild hepatic or renal impairment appear to have no effect on the pharmacokinetics of the drug but the effect of severe impairment is unknown. Depressed mood disorders have been observed with rimonabant but adverse events are relatively benign consisting of nausea, dizziness, anxiety, diarrhea and insomnia. More studies are needed to evaluate the clinical significance of psychiatric adverse events, the leading cause of treatment discontinuation, associated with use of rimonabant. Since rimonabant is metabolized by the CYP3A hepatic enzyme system, possible drug interactions would include inhibitors and inducers of this enzyme system.

If approved, rimonabant would be the first CB1 receptor antagonist approved for long-term use in obesity and studies are currently underway to evaluate its role for other indications. Ongoing clinical studies, cost and further clinical experience will determine the clinical application of this drug.
Drug Information Highlights

- **Compounded Topical Anesthetic Creams**: Standardized versions of topical anesthetic creams, marketed for general distribution, present serious public health risks. The FDA has issued warning letters to five firms to stop compounding and distributing such products often used to lessen pain associated with such procedures as laser hair removal, tattoos and skin treatments. Exposure to high concentrations of local anesthetics, as exist in these products, may cause serious adverse reactions such as seizures, irregular heartbeats and death.

- **Heparin Sodium Injection**: The WARNINGS section of the prescribing information for Heparin has been revised to include information on the possibility of delayed onset of heparin-induced thrombocytopenia (HIT), a serious antibody-mediated reaction resulting from irreversible aggregation of platelets. HIT may progress to heparin-induced thrombocytopenia and thrombosis (HITT), a condition of venous and arterial thromboses. The initial presentation for HITT may be thrombotic events and can occur up to several weeks after the discontinuation of heparin therapy.

- **Quinine Products**: The FDA has ordered a halt to manufacturing of unapproved products containing quinine due to safety concerns and inadequate labeling. Qualaquin™ is the only FDA-approved quinine product indicated for treatment of certain types of malaria without complications. Quinine is also commonly prescribed to prevent or treat leg cramps. The FDA is cautioning against this off-label use due to risks associated with the drug such as cardiac arrhythmias, thrombocytopenia and severe hypersensitivity reactions. These risks are justified for treatment of malaria due to its life-threatening nature.

- **Aprotinin Injection (Trasylol®)**: Trasylol® is now indicated only for use in patients at increased risk for blood loss and blood transfusion in association with cardiopulmonary bypass in the course of coronary artery bypass grafting. Administration should be only in the operative setting where cardiopulmonary bypass can be rapidly initiated. Treatment with Trasylol® increases the risk for renal dysfunction and may increase the need for dialysis postoperatively. The drug is contraindicated in patients with known or expected exposure to it in the previous twelve months due to increased risk of anaphylactic reactions.

- **Rituximab (Rituxan®)**: Emerging safety information indicates that two patients have died after treatment with rituximab for systemic lupus erythematosus (SLE). A viral infection of the brain called progressive multifocal leukoencephalopathy (PML), caused by reactivated JC virus present in approximately 80 percent of adults was the cause of death. Physicians should closely monitor patients treated with rituximab for development of PML.

### FDA New Drug Approvals

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Description</th>
<th>Applicant</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone</td>
<td>Invega</td>
<td>The principle active metabolite of risperidone, a dibenzapine derivative antipsychotic agent, approved for the treatment of schizophrenia.</td>
<td>Ortho McNeil Janssen</td>
<td>FDA approved on 12-20-2006</td>
</tr>
</tbody>
</table>

### FDA Approved New Indications for Existing Products

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Description</th>
<th>Applicant</th>
<th>FDA Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>Celebrex</td>
<td>A COX-2 selective non-steroidal anti-inflammatory drug (NSAID) now approved for the relief of the signs and symptoms of Juvenile Rheumatoid Arthritis (JRA) in patients two years of age and older.</td>
<td>Pfizer</td>
<td>FDA approved new indication on 12-15-2006</td>
</tr>
<tr>
<td>Balsalazine disodium</td>
<td>Colazal</td>
<td>A compound delivered intact to the colon where it is cleaved by bacterial azoreduction to release mesalamine, the therapeutically active portion of the molecule, for treatment of mildly to moderately active ulcerative colitis. Previously approved only for use in adult patients, the compound is now approved for treatment of patients five to seventeen years of age.</td>
<td>Salix Pharmaceuticals</td>
<td>FDA approved new indication on 12-20-2006</td>
</tr>
</tbody>
</table>