CAREMARK TrendsRx® Drug Pipeline&News

April 21, 2006
Volume 2, Issue Number 8
Pipeline Highlights from March 31, 2006 - April 13, 2006 and Recent Selected Healthcare News Highlights

A bi-weekly publication highlighting recent events in the pharmaceutical industry

Pipeline

Recent New Drug Application (NDA) Submissions[1]*

Product Description	Indication(s)	Submission Date	Route of Administration	Comments
ACTO*plus* met XR (pioglitazone/metformin) Takeda Pharmaceutical Company	Treatment of type 2 diabetes	April 3, 2006	Oral Extended-release	This is a once-daily product.
RSD1235 Cardiome Pharma Corp./ Astellas Pharma US, Inc.	Acute conversion of atrial fibrillation (AF)	March 31, 2006	Injection - intravenous	A trade name has not yet been determined.
Saforis™ (glutamine in UpTec™) MGI Pharma, Inc.	Prevention and treatment of oral mucositis in patients receiving mucotoxic cancer therapy	April 13, 2006	Oral - powder for suspension	Saforis is designed to deliver high concentrations of the amino acid glutamine into damaged oral mucosa to promote healing.

Recent Product Launches[1]*

Product Description	Indication(s)	Launch Date†	Route of Administration	Comments
Taclonex® (calcipotriene 0.005% and betamethasone dipropionate 0.064%) LEO Pharma/Warner Chilcott	Topical treatment of psoriasis vulgaris in adults 18 years of age and above for up to four weeks	April 3, 2006	Topical - ointment	This product is applied once-daily for up to four weeks.

Recent New Drug Application (NDA) Approvals[1]*

Product Description	Indication(s)	Approval Date	Launch Date†	Route of Administration	Comments
Daytrana™ (methylphenidate) 10 mg, 15 mg, 20 mg, 30 mg Noven Pharmaceuticals, Inc./ Shire US Inc.	Treatment of Attention Deficit Hyperactivity Disorder (ADHD)	April 6, 2006	Second quarter 2006	Topical - transdermal patch	This is a new formulation of an already approved product. This is a once-daily formulation. Daytrana is classified as a Schedule II controlled substance.
Prograf® (tacrolimus) Injection 5 mg/mL; capsules 0.5 mg, 1 mg, 5 mg Astellas Pharma US, Inc.	Prevent organ rejection in patients who have received a heart transplant	March 29, 2006	March 29, 2006	Oral - capsule Injection - intravenous infusion	This is a new indication for an already approved product. The product is also approved for the prevention of organ rejection in liver and kidney transplants.

First Generic Product Approvals/Launches[1]*

Generic Product Description	Reference Brand	Dosage Form, Strength(s)	Final Approval Date‡	Launch Date†	Comments
mitoxantrone	Novantrone®	Injection, 2 mg/mL	April 11, 2006	April 2006	The reference brand is used in the treatment of secondary (chronic) progressive, progressive relapsing, or worsening relapsing-remitting multiple sclerosis; hormone-refractory prostate cancer; and acute nonlymphocytic leukemia in adults.
pilocarpine	Salagen®	Tablets, 7.5 mg	April 5, 2006	To be determined	The reference brand is used in the treatment of dry mouth. This product is AB-rated.

* Adapted from RxPipeline Services Week in Review. For more information contact: pipeline@caremark.com<mailto:pipeline@caremark.com>
† This anticipated launch date may not reflect the date of availability for this medication. Due to circumstances beyond the control of Caremark, information related to prospective medication launch dates is subject to change without notice. This information should not be solely relied upon for decision-making purposes.
‡ The Final Approval Date is established by the FDA, but does not necessarily mean a generic product is available as of that date, or that such product is available.

Selected Phase III Clinical Trials

Silenor™ (doxepin) Evaluated in the Treatment of Chronic Insomnia[2]

On April 10, 2006, Somaxon Pharmaceuticals, Inc. released results from a Phase III trial on Silenor, an investigational medication for the treatment of adults with primary insomnia. The 35-day randomized, double-blind, placebo-controlled, parallel-group, multicenter trial assessed the safety and efficacy of Silenor 3 mg and 6 mg in 229 adults with chronic primary insomnia. The primary endpoint for the trial was eight-hour Wake After Sleep Onset (WASO), which is a measure of sleep maintenance. When compared to placebo, Silenor 3 mg and 6 mg showed a statistically significant mean improvement of 26 minutes and 31 minutes, respectively, in WASO. Improvement in Total Sleep Time (TST) was significantly improved for both doses of Silenor at the initial treatment period, with Silenor 3 mg increasing TST to 415 minutes and Silenor 6 mg increasing TST to 421 minutes, compared with 374 minutes for placebo. This result was statistically significant and remained statistically significant for both doses after four weeks of therapy.

Both doses of Silenor were well tolerated. Rebound insomnia, withdrawal effects, memory impairment, weight gain, and anticholinergic effects (eg, drowsiness, dry eyes, dry mouth) were not observed during the treatment period. There were no reports of tolerance to Silenor during the trial.

Silenor is a low-dose formulation of doxepin. Higher doses of doxepin have been prescribed for the treatment of anxiety and depression. Currently available products promote sleep by working at the benzodiazepine, or GABA, receptors in the brain. Silenor, however, blocks histamine, which has been shown to reduce wakefulness and is thought to encourage the initiation and maintenance of sleep.

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Somaxon anticipates reporting additional Phase III results for Silenor later this year and plans to file a New Drug Application (NDA) for this product in the first quarter of 2007.

Rotigotine Transdermal Patch Improves Symptoms of Early-Stage Parkinson's Disease (PD)[3]

On April 6, 2006, Schwarz Pharma presented results from an open-label extension of a Phase III trial of the rotigotine transdermal patch (Neupro®) at the 58th Annual Meeting of the American Academy of Neurology. The original double-blind, placebo-controlled study included 273 patients with early-stage PD who were randomized to treatment with rotigotine or placebo for six months. Patients on rotigotine therapy showed an average improvement of 3.8 points in their Unified Parkinson Disease Rating Scale (UPDRS) scores compared to the placebo group, whose scores worsened by an average of 1.5 points from baseline.

In an open-label extension to the study mentioned above, patients who had completed six months of double-blind treatment were eligible for study inclusion. Of the 216 patients at the initiation of the open-label phase, 208 patients had efficacy data. Before entering a maintenance treatment phase, patients were treated over a three-week period using rotigotine therapy in doses ranging from 2 mg/24 h (10 cm^2) to 6 mg/24 h (30 cm^2). Dose increases of up to a total of 16 mg/24 h (80 cm^2) were allowed after one year of open-label treatment.

Efficacy was measured using UPDRS Parts II and III, which evaluate motor systems of Parkinson's disease and a patient's ability to perform everyday activities. The UPDRS scores were compared with the baseline scores collected in the original double-blind trial. The results revealed that early initiation of rotigotine may have a long-term advantage. Early in the open-label extension, a similar percentage of patients from the original treatment groups achieved a 20% or greater reduction in their UPDRS scores. Also, 31% of patients who remained on rotigotine from the start of double-blind treatment maintained improvement on UPDRS for at least 85 weeks versus 20% of patients originally randomized to placebo.

Rotigotine is a non-ergolinic dopamine receptor agonist that behaves like dopamine in the body. Schwarz Pharma received an approvable letter for rotigotine from the FDA on February 28, 2006.

News

Medication Safety

Information regarding select medication safety issues can be found on the Caremark Web site at: www.caremark.com>For Health Professionals>Drug Safety Alerts

Macugen® (pegaptanib) Labeling Changes[4]

On April 7, 2006, the FDA released a MedWatch alert to notify healthcare professionals of changes to the Macugen [(OSI)™ Eyetech Inc. and Pfizer Inc.] labeling. These changes were made in response to rare reports of anaphylaxis/anaphylactoid reactions, including angioedema. Changes have been made to the *Contraindications, Precautions, Adverse Events Postmarketing*, and *Dosage and Administration* sections of the labeling. The manufacturer and the FDA are recommending that healthcare professionals evaluate the patient's medical history for hypersensitivity reactions to Macugen before using this product.

Macugen is indicated for the treatment of wet age-related macular degeneration and is administered once every six weeks by injection into the eye.

Selected Healthcare News

Study Compares Lovenox® (enoxaparin) and Arixtra® (fondaparinux) in Patients with Acute Coronary Syndromes (ACS)[5]

The April 6, 2006, issue of *The New England Journal of Medicine* includes results from the OASIS 5 (the Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) trial. In this double-blind, double-dummy, multicenter trial, 20,078 patients with ACS were randomly assigned to receive Arixtra (GlaxoSmithKline) 2.5 mg daily or Lovenox (sanofi-aventis) 1 mg/kg twice daily for a mean of six days. The objective of the study was to demonstrate the noninferiority of Arixtra as compared with Lovenox at nine days. The primary efficacy outcome was death, heart attack, or refractory ischemia. The primary safety outcome was major bleeding at nine days. Patients were followed for 90 days to 180 days.

The number of patients with primary efficacy outcome events was similar between the two treatment groups, which confirms the noninferiority of Arixtra as compared to Lovenox. According to the authors, there was a trend toward a lower rate of death, heart attack, or refractory ischemia with Arixtra than with Lovenox at 30 days. This result may have been due to a statistically significant reduction in mortality that was observed with Arixtra. The rate of major bleeding at nine days

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was lower with Arixtra than Lovenox. This result was statistically significant and continued during the follow-up period. The authors concluded that Arixtra is similar to Lovenox in reducing the risk of ischemic events at nine days, and Arixtra therapy reduces major bleeding and improves long-term mortality and morbidity.

Human Papillomavirus (HPV) Vaccine Found to Have Continued Efficacy in a Follow-Up Trial[1,6]

On April 6, 2006, an early online publication of *The Lancet* included results from a follow-up study of a multicenter, randomized, double-blind, placebo-controlled trial involving Cervarix™, a bivalent HPV-16/18 virus-like particle AS04 vaccine manufactured by GlaxoSmithKline/MedImmune. The follow-up study included 776 women who received the complete three-dose regimen during the initial trial.

In the follow-up study, more than 98% of the patients who received Cervarix were shown to have antibodies to HPV types 16 and 18 at every timepoint during the extended follow-up phase. HPV types 16 and 18 are most commonly associated with HPV infections and the precursors of cervical cancer associated with HPV infections. Significant long-term efficacy was shown against HPV-16/18 infections up to a mean of 42 months after the scheduled doses of Cervarix were given. After evaluating the initial study and the extended follow-up study, the authors noted high levels of vaccine efficacy up to a mean of 47.7 months after entry into the study. The authors concluded that Cervarix is highly immunogenic and safe. The authors also concluded that Cervarix provides a high level of protection against HPV-16/18 infections and the associated cervical lesions up to 4.5 years. There was also data to show protection against infection with some other types of HPV.

Cervarix is currently in Phase III trials for the prevention of cervical cancer caused by HPV. Approval and launch of this product are expected in the fourth quarter of 2007.

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