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Pipeline Highlights from March 17 - March 30, 2006 and Recent Selected Healthcare News Highlights

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

Pipeline

Phase III Clinical Trials

Pivotal Trial Results Released for Lacosamide in Epilepsy¹

On March 29, 2006, Schwarz Pharma released results from the first Phase III trial of oral lacosamide for the adjunctive treatment of epilepsy. In this multicenter, double-blind, placebo-controlled trial, 485 patients with partial seizures who suffered from refractory epilepsy were randomized to receive adjunctive (add-on) treatment with placebo, 200 mg/day of lacosamide, or 400 mg/day of lacosamide. This trial included a four-week titration phase and a 12-week maintenance phase. The primary endpoints of the study were reduction of seizure frequency and a 50% response to treatment (a 50% reduction in seizures).

When compared to baseline, the lacosamide 200 mg/day and 400 mg/day regimens significantly reduced seizure frequency more than placebo. When “responders” (patients with a 50% seizure reduction from baseline to maintenance endpoint) were analyzed, there was a statistically significant difference between placebo and the lacosamide 400 mg/day treatment groups. The most common side effects seen with lacosamide therapy were dizziness, nausea, and vomiting.

Lacosamide is an anticonvulsant medication. The oral medication was given twice daily in clinical trials; an intravenous formulation is in development. This medication is also currently in Phase III trials for the treatment of diabetic neuropathic pain.

First Generic Product Approvals/Launches^{2*}

| Generic Product Description | Reference Brand | Dosage Form, Strength(s) | Final Approval Date [†] | Launch Date [‡] | Comments |
|-----------------------------|------------------------|----------------------------|----------------------------------|--------------------------|--|
| terconazole | Terazol [®] 3 | Vaginal suppository, 80 mg | March 17, 2006 | March 2006 | The reference brand is used in the treatment of vaginal yeast infections. This product is AB-rated. |
| zidovudine | Retrovir [®] | Capsule, 100 mg | March 27, 2006 | To be determined | The reference brand, in combination with other antiretroviral agents, is used in the treatment of human immunodeficiency virus infection. This product is AB-rated. |



Recent Supplemental New Drug Application (sNDA) Approvals^{2*}

| Product Description | Indication(s) | Approval Date | Launch Date [‡] | Route of Administration | Comments |
|---|---|-------------------|--------------------------|----------------------------------|--|
| Flovent [®] HFA (fluticasone) 44 mcg, 110 mcg, 220 mcg GlaxoSmithKline | Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older | February 28, 2006 | February 2006 | Inhalation - aerosol | This approval expands the patient population for this medication to children four years of age and older. Flovent HFA was originally approved on May 14, 2004, for the maintenance treatment of asthma as preventative therapy in patients 12 years of age and older. |
| Relenza [®] (zanamivir) GlaxoSmithKline | In adults and pediatric patients 5 years of age and older for the prophylaxis of influenza | March 29, 2006 | March 29, 2006 | Inhalation - dry powder inhaler | This is a new indication for an already approved product. Relenza was previously approved for the treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients seven years and older who have been symptomatic for no more than two days. Relenza is not a substitute for the flu vaccine, which is the primary means of preventing flu infection. |
| Taxotere [®] (docetaxel) 20 mg/0.5 mL, 80 mg/2 mL sanofi-aventis | In combination with cisplatin and 5-fluorouracil: Treatment of patients with advanced stomach (gastric) cancer, including cancer of the gastroesophageal (GE) junction, who have not received prior chemotherapy for advanced disease | March 22, 2006 | March 22, 2006 | Injection - intravenous infusion | New indication for an already approved product. This product received Priority Review and is also used in the treatment of cancers of the lung, prostate, and breast. |

Recent New Drug Application (NDA) Approvals^{2*}

| Product Description | Indication(s) | Approval Date | Launch Date [‡] | Route of Administration | Comments |
|--|---|----------------|--------------------------|-------------------------|--|
| YAZ [®] (3 mg drospirenone/ 20 mcg ethinyl estradiol) Berlex Laboratories | Prevention of pregnancy in women who elect to use an oral contraceptive | March 16, 2006 | April 2006 | Oral - tablet | This is a new formulation for an already approved product. This product contains 24 days of active hormone and four days of placebo. |
| Zegerid [®] with Magnesium Hydroxide (omeprazole/ sodium bicarbonate/ magnesium hydroxide) 20 mg/600 mg/700 mg and 40 mg/600 mg/700 mg Santarus, Inc. | Treatment of heartburn and other symptoms associated with GERD (gastroesophageal reflux disease), erosive esophagitis, duodenal ulcers and gastric ulcers | March 24, 2006 | 2007 | Oral - chewable tablet | This is a new formulation for an already approved product. |

Recent Product Launches^{2*}

| Product Description | Indication(s) | Launch Date [†] | Route of Administration | Comments |
|--|---|--------------------------|----------------------------------|---|
| Zegerid [®] (omeprazole/sodium bicarbonate) 20 mg/1100 mg, 40 mg/1100 mg Santarus, Inc. | Treatment of heartburn and other symptoms associated with GERD, the short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy, the short-term treatment (4-8 weeks) of active benign gastric ulcer, the short-term treatment of active duodenal ulcer, and to maintain healing of erosive esophagitis | March 28, 2006 | Oral - immediate-release capsule | None |
| Ranexa [™] (ranolazine) 500 mg CV Therapeutics, Inc. | Treatment of chronic angina | March 24, 2006 | Oral - extended-release tablet | Ranexa is approved as second-line treatment for chronic angina and has antianginal properties and anti-ischemic effects that are not dependent on reductions in heart rate or blood pressure. |

* Adapted from RxPipeline Services Week in Review. For more information contact: pipeline@caremark.com<mailto:pipeline@caremark.com>

† 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.

‡ 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.

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

Public Health Advisory Issued Regarding Safety Issues with the Diastat[®] AcuDial[™] (diazepam rectal gel)³

On March 30, 2006, the U.S. Food and Drug Administration (FDA) issued a Public Health Advisory regarding Diastat AcuDial (Valeant Pharmaceuticals). This product is administered rectally and is used for the at-home treatment of seizures. The Public Health Advisory stated that the manufacturer has received over one hundred complaints regarding cracks in the plastic tip of the Diastat applicators. These cracks may result in leakage of the medication when the plunger is depressed; therefore, the patient may not receive the full dose of medication. Complaints were received for the Diastat AcuDial 10 mg and 20 mg applicators; no complaints have been received for the 2.5 mg product.

Healthcare professionals should advise patients on Diastat therapy of this issue. Syringes should be checked for cracks on a monthly basis; specific instructions on how to check for cracks can be found at <http://www.diastat.com> or by calling Valeant Pharmaceuticals toll-free at 1-877-361-2719. If seizures continue after using Diastat AcuDial therapy, emergency medical help should be obtained immediately by calling 911 or an ambulance. The manufacturer is working to correct the applicator problem, but new Diastat syringes will not be available until June or July 2006. The “old” prefilled syringes will continue to be dispensed until that time because no other at-home product is available to treat this condition.

This medication safety issue has been reviewed and was addressed by the Caremark Drug Safety Alert (DSA) program.

FDA Advisory Committee Meetings

Note: The FDA Advisory Committees provide recommendations to the FDA. However, the FDA is not bound by the recommendations of its Advisory Committees.

Medications for Attention Deficit Hyperactivity Disorder (ADHD) Reviewed by Pediatric Advisory Committee⁴

On March 22, 2006, the FDA's Pediatric Advisory Committee reviewed selected safety issues regarding medications used for the treatment of ADHD. This is the second advisory committee to discuss this issue as the Drug Safety & Risk Management Advisory Committee met in February to suggest that a black box warning regarding the risk of cardiovascular adverse events be added to the labeling for ADHD medications in adults.

The Pediatric Advisory Committee found that potential episodes of psychosis, aggression, and cardiac events in children did not justify a black box warning. The committee felt that the risk of cardiovascular events was not similar for adults and children, except for those persons with cardiovascular abnormalities. The committee also did not support a black box warning for psychiatric events (eg, suicidality) and suggested that this information be discussed in the *Warnings* section of the labeling.

The committee recommended that the language regarding cardiovascular risk currently included in the labeling for amphetamine medications be included in the labeling of all ADHD medications. In addition, the committee recommended that a Medication Guide that discusses the potential for psychiatric risks, cardiovascular risks, and aggression, be added to the labeling. The committee's recommendations apply to all ADHD medications, regardless of whether or not they are classified as stimulants.

FDA Advisory Committee Votes Against Approving Sparlon™ (modafinil)—Additional Safety Data Needed^{5,6}

On March 23, 2006, the FDA's Psychopharmacologic Drugs Advisory Committee recommended against approving Sparlon for the treatment of ADHD in children and adolescents by a vote of 12 to 1. Sparlon is an investigational formulation and proprietary dosage strength of modafinil, an ingredient which is currently marketed as Provigil® (manufactured by Cephalon).

The committee stated that Cephalon had not presented sufficient safety data regarding the use of Sparlon in children with ADHD and recommended that the manufacturer conduct a pre-approval safety study to determine the risk of serious skin reactions. The committee voted unanimously that Sparlon is efficacious for the treatment of ADHD.

The committee's safety debate focused on one case of suspected Stevens Johnson Syndrome (SJS) seen in the modafinil clinical trials and four cases of suspected SJS from post-marketing data in three million adult patients. SJS is a potentially fatal skin reaction that occurs in approximately one out of one million people. The committee also discussed the Sparlon dose being proposed by Cephalon. The proposed dose is higher than that used in adult patients for excessive sleepiness, and the medication's safety has not been previously demonstrated in younger patients.

In October 2005, the FDA issued an approvable letter for Sparlon. In addition, the FDA has indicated that the medication's potential risk for SJS would most likely require a black box warning.

Selected Healthcare News

FDA Extends Tysabri® (natalizumab) Review Time⁷

On March 22, 2006, Biogen Idec and Elan announced that the FDA had extended the regulatory review period for the reintroduction of Tysabri for multiple sclerosis (MS) by up to 90 days.

The FDA will use this additional time to review the revised Risk Management Plan (RMP), which takes into account the recommendations of the Peripheral and Central Nervous System Drugs Advisory Committee. Both the company and the FDA believe that a RMP is important to ensure safe use of the product. The FDA has stated that the Tysabri application continues to be a high priority. The FDA is working to complete a review of this new information and will attempt to do so before the end of the 90 day extension period.

New Strategies for Treating Depression⁸⁻¹⁰

Data from the nation's largest depression study show that one in three depressed patients who previously did not achieve an absence of symptoms (remission) using an antidepressant became symptom-free with the help of an additional medication, and one in four achieved remission after switching to a different antidepressant. According to the authors, data from the study show that people whose depression is resistant to initial treatment can achieve remission by adding an additional medication to existing therapy or switching antidepressant medications. This is the first study to examine the effectiveness of different treatment strategies for patients who were not symptom-free after an initial trial of medication.

The study was funded by the National Institute of Mental Health, part of the National Institutes of Health. Results of the STAR[®]D study were examined in two papers published in the March 23, 2006, issue of *The New England Journal of Medicine*.

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