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Pipeline Highlights from March 3 - March 16, 2006 and Recent Selected News Highlights

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

Pipeline

Selected Phase III Clinical Trials

Baraclude™ (entecavir) Shows Benefit Over Lamivudine in Treating Patients with Hepatitis B Virus (HBV)¹⁻³

On March 8, 2006, Bristol-Myers Squibb Company announced that two studies published in *The New England Journal of Medicine* showed that Baraclude, a nucleoside analog, demonstrated greater benefit in treating nucleoside-naïve chronic HBV-infected patients compared to lamivudine (EpiVir-HBV®, GlaxoSmithKline). Baraclude is indicated for the treatment of chronic HBV infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

Two randomized, multinational, Phase III clinical trials found that Baraclude treatment resulted in statistically significantly greater improvements in liver histology and reductions of HBV DNA to undetectable levels compared to treatment with lamivudine in both nucleoside-naïve hepatitis B e-antigen (HBeAg)-positive and HBeAg-negative chronic hepatitis B patients at 48 weeks. HBV rebound due to resistance to Baraclude was not detected in either study. Approximately 400 million people worldwide are infected with HBV. Only a small percentage of these patients are treated with prescription medication.

Recent New Drug Application (NDA) Submissions^{4*}

Product Description	Indication(s)	Submission Date	Route of Administration	Comments
Alvesco® (ciclesonide) ALTANA Pharma US, Inc./ sanofi-aventis	Treatment of nasal symptoms associated with seasonal and perennial allergic rhinitis	March 7, 2006	Intranasal - nasal spray	According to the American Academy of Allergy Asthma & Immunology, over 40 million people in the United States suffer from allergic diseases. Allergies are the sixth leading cause of chronic disease in the United States.



Recent Supplemental New Drug Application (sNDA) Approvals^{4*}

Product Description	Indication(s)	Approval Date	Launch Date [†]	Route of Administration	Comments
Vanos™ (fluocinonide) 0.1% Medicis	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years of age and older	March 2, 2006	March 2, 2006	Topical - cream	This is an expanded indication for an already approved product. Vanos was launched in April 2005 for the treatment of plaque-type psoriasis.

* 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.

News

Selected Medication Safety Issues

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

Medical Device Correction: BD Logic[®], BD Latitude[™], Paradigm Link[®] Blood Glucose Meters⁵

In January 2006, BD Medical notified patients of issues in the displaying of test results with the BD Logic, BD Latitude, and Paradigm Link blood glucose meters. In the United States, blood glucose meters display test results in “milligrams per deciliter” (mg/dL). In some other countries, blood glucose meters may display test results in “millimoles per liter” (mmol/L). On rare occasions the BD Logic, BD Latitude, and Paradigm Link blood glucose meters may switch the blood glucose test result display from “mg/dL” to “mmol/L” (for example, when a battery is installed or the meter is dropped). This may cause a patient to misinterpret his/her blood glucose results.

Patients with affected blood glucose meters should call BD toll-free at 1-866-556-8123. If the meter correctly displays results in “mg/dL”, there is no need to contact BD, and patients may continue to use their meter as directed.

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

FDA Advisory Committee Meetings

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

Tysabri[®] (natalizumab) Return to U.S. Market Supported by Advisory Committee^{4,6-11}

The U.S. Food and Drug Administration’s (FDA’s) Peripheral & Central Nervous System Drugs Advisory Committee met on March 7 to 8, 2006 to discuss the return of Tysabri (Biogen Idec and Elan Pharmaceuticals) to the U.S. market. The first-line use of Tysabri in patients with relapsing forms of multiple sclerosis (MS) was recommended by the Advisory Committee by a vote of seven to five. The Committee voted in favor of making Tysabri available to patients with MS who had not tried any of the other available first-line therapies for MS (eg, Avonex[®] (interferon beta-1a), Biogen Idec; Rebif[®] (interferon beta-1a), Serono Inc.; Betaseron[®] (interferon beta-1b), Berlex Laboratories; Copaxone[®] (glatiramer), Teva Pharmaceuticals). The Committee recommended that the medication be made available only to patients with relapsing MS, despite the patient’s degree of disability.

The Committee was in agreement that, upon return to the U.S. market, Tysabri should not be used with other available MS medications. The Committee also agreed that the patient and physician registry proposed by Biogen Idec should be mandatory. The registry is part of a risk management program proposed by the manufacturer.

This product was originally approved in November 2004 by the FDA for the treatment of individuals with relapsing forms of MS to reduce the frequency of clinical exacerbations. In February 2005, Tysabri was voluntarily removed from the market by the manufacturers and was suspended from use in clinical trials based on reports of three cases of progressive multifocal leukoencephalopathy. Tysabri uses a different mechanism to prevent relapses than currently available agents to prevent MS exacerbations. It is the first medication in a new class called the selective adhesion molecule (SAM) inhibitors. Tysabri is thought to act by preventing the movement of possibly harmful immune cells from the bloodstream into the central nervous system.

On March 22, 2006, Biogen Idec and Elan Pharmaceuticals announced that the FDA had extended its regulatory review of Tysabri by up to 90 days; action by the FDA is anticipated on or before June 28, 2006.

FDA Advisory Committee Finds Gemzar[®] (gemcitabine) Ovarian Cancer Data Insufficient for Approval in Recurrent Disease¹²

On March 13, 2006, the FDA’s Oncologic Drugs Advisory Committee found that data from the Gemzar (Eli Lilly and Company) ovarian cancer study are not strong enough to warrant approval of the agent in patients whose disease has recurred. The manufacturer is pursuing an indication for Gemzar in combination with carboplatin for the treatment of patients with advanced ovarian cancer that has relapsed for at least six months after completion of platinum-based therapy.

The Advisory Committee was concerned with data that showed Gemzar plus carboplatin increased progression-free survival of ovarian cancer by a median 2.8 months compared to carboplatin alone (8.6 months vs. 5.8 months); however, there was no difference between the two arms in overall survival. The study was conducted outside of the United States in Europe and other countries around the world. Therefore, it is

difficult to interpret how the data could be extrapolated to clinical care settings in the United States.

Gemzar is currently approved for cancers of the breast, non-small cell lung, and pancreas.

Selected Healthcare News

Plavix® (clopidogrel) Study Finds that Certain Subgroups of Patients May Benefit from Dual Therapy, For Others It Should Be Avoided¹³⁻¹⁵

On March 12, 2006, Bristol-Myers Squibb Company released results from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial which showed that certain patients may benefit from combined Plavix and aspirin therapy, while others may not. In this study, the combination of the antiplatelet agents Plavix and aspirin did not demonstrate a statistically significant reduction in the risk of heart attack, stroke, or cardiovascular death compared to placebo and aspirin in patients with established atherothrombotic disease or multiple risk factors for atherothrombotic events. Analysis of the two main patient subgroups showed different responses to Plavix and aspirin therapy. Plavix is approved for early and long-term risk reduction in patients at risk for atherothrombotic events.

Patients with multiple risk factors, but no clearly established vascular disease, did not benefit from the addition of Plavix to aspirin. These patients represented approximately 20% of the overall study population. In this patient subgroup, there was an excess in cardiovascular mortality, as well as a non-statistically significant increase in bleeding observed in patients treated with Plavix and aspirin.

In patients with established atherothrombotic disease (also referred to as “secondary prevention”), the CHARISMA trial findings showed that Plavix, in addition to aspirin and other standard therapy, significantly reduced the relative risk of a recurrent heart attack, stroke, or cardiovascular death compared to patients receiving placebo and aspirin. This result was statistically significant. These patients accounted for nearly 80% of the total CHARISMA study population.

The American College of Cardiology advises patients on Plavix therapy to consult with their healthcare provider or cardiologist. Results from the CHARISMA study may be misinterpreted by some patients, which may lead them to inappropriately stop their Plavix anti-clotting therapy. Although certain patients may not benefit from Plavix and aspirin therapy, the CHARISMA study does not invalidate the use of Plavix for approved indications (eg, stenting, after a

heart attack or stroke). Patients should discuss the risks and benefits of Plavix therapy with their healthcare provider. In patients with recently-placed stents, stopping Plavix therapy may lead to clot formation within the stent, which may result in serious harm or death.

Crestor™ (rosuvastatin) Shows Regression of Coronary Artery Disease (CAD)¹⁶

On March 13, 2006, AstraZeneca International released data from ASTEROID (A Study To Evaluate the Effect of Rosuvastatin On Intravascular Ultrasound-Derived Coronary Atheroma Burden), a two-year, open-label, single-arm, blinded endpoint study that evaluated the effects of Crestor 40 mg in 507 patients who had undergone coronary angiography and who had evidence of CAD. These data were presented at the 55th Annual Scientific Session of the American College of Cardiology and showed that artery plaque build-up was reduced between 6.8% to 9.1%. These changes were associated with reductions in LDL (“bad” cholesterol) and increases in HDL (“good” cholesterol).

Crestor is used in the treatment of high cholesterol. Crestor is not indicated for atherosclerosis. Crestor 40 mg is the highest approved dose of Crestor; this product should be used according to the full prescribing information.

References:

1. *The New England Journal of Medicine* reports Baraclude (entecavir) demonstrated benefits over lamivudine in treating chronically infected hepatitis B patients at 48 weeks [press release]. Princeton, NJ: Bristol-Myers Squibb Company; March 8, 2006. Available at: http://www.bms.com/news/press/data/fg_press_release_6261.html. Accessed March 10, 2006.
2. Lai C, Shouval D, Lok AS, et al. Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. *New Eng J Med* 2006; 354 (10): 1011-1020.
3. Chang T, Gish RG, de Man R, et al. A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *New Eng J Med*. 2006; 354 (10): 1001-1010.
4. Caremark. RxPipeline Insider. Available at: www.rxpipelineinsider.com. Accessed March 10, 2006 and March 17, 2006.
5. Urgent medical device correction: BD Logic®, BD Latitude®, Paradigm Link® Blood Glucose Monitors [press release]. Bridgeport, CT: BD Medical; January 2006. Available at: http://www.bddiabetes.com/us/bgm_notice.asp. Accessed March 14, 2006.
6. Tysabri [package insert]. Cambridge, MA: Biogen Idec Inc.; November 2004.
7. Drugs@FDA- Label and Approval History: Tysabri. Food and Drug Administration Web site. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Accessed March 15, 2006.
8. National Multiple Sclerosis Society. FDA Advisory Committee Recommends Tysabri's Return to Market. Available at: <http://www.nationalmssociety.org/tysabri.asp>. Accessed March 15, 2006.
9. FDA Advisory Committee. Tysabri return to market: first-line use in relapsed MS supported by slim committee majority. Available at: http://www.fda.gov/oc/ohrt/2006/FDAAdvisoryCommittee/FDCAdvisoryCommittee/Committees/Peripheral+and+Central+Nervous+System+Drugs/030706_tysabri/030806_tysabriR.htm. Accessed March 14, 2006.
10. Antegen may hold promise as effective new MS treatment [press release]. Multiple Sclerosis Foundation; January 8, 2003. Available at: http://www.msfacts.org/news/n_jan03.html. Accessed March 17, 2006.
11. Biogen Idec and Elan announce that FDA will extend regulatory review period for the reintroduction of Tysabri® for multiple sclerosis [press release]. Cambridge, MA and Dublin, Ireland: Biogen Idec Inc.; March 22, 2006. Available at: http://www.biogenidec.com/site/019_0.html?pr_id=.../news/BiogenIDECPR_117.htm. Accessed March 22, 2006.
12. FDA Advisory Committee. Gemzar ovarian cancer data not sufficient for approval in recurrent disease, cmte says. Available at: http://www.fda.gov/oc/ohrt/2006/FDAAdvisoryCommittee/Committees/Oncologic+Drugs/031306_Gemzar/031306_GemzarR.htm. Accessed March 15, 2006.
13. New Study Furthers Understanding Of The Role Of Dual Antiplatelet Therapy In The Prevention Of Atherothrombotic Events, Including Heart Attack, Stroke Or Cardiovascular Death In Broad Population [press release]. Paris, France and Princeton, NJ: Bristol-Myers Squibb Company; March 12, 2006. Available at: http://www.bms.com/news/press/data/fg_press_release_6264.html. Accessed March 15, 2006.
14. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin alone for the prevention of atherothrombotic events. *New Eng J Med*. 2006; 354: 1-12.
15. Public Health Alert: Dangers of stopping clopidogrel (Plavix®) for patients with stents and certain other conditions [press release]. American College of Cardiology; March 16, 2006. Available at: <http://www.acc.org/Charisma%20Health%20Alert.pdf>. Accessed March 17, 2006.
16. First statin to show regression of coronary artery disease in a major clinical study [press release]. AstraZeneca International; March 13, 2006. Available at: <http://www.astrazeneca.com/pressrelease/5228.aspx>. Accessed March 13, 2006.

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