CAREMARK TrendsRx® Drug Pipeline&News

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Pipeline

Phase III Clinical Trials

Pivotal Trial Shows New Formulation of FluMist® (Influenza Vaccine Live, Intranasal) Significantly Reduces Influenza (flu) Illness When Compared to the Flu Shot in Children Aged 6 Months Through 59 Months[1]

On December 12, 2005, MedImmune, Inc. released preliminary results from a randomized, double-blind, double-dummy, multicenter Phase III study involving CAIV-T (cold adapted influenza vaccine, trivalent), an investigational formulation of FluMist that can be kept in the refrigerator instead of the freezer. The study occurred during the 2004–2005 flu season and enrolled 8,492 children aged 6 months through 59 months at 249 sites in 16 countries in North America, Europe, and Asia. Patients received either CAIV-T or the flu shot. The flu rate for patients receiving the flu shot was 8.6% compared to 3.9% for those who received CAIV-T ($p<0.0001$). The rate of side effects was similar in the two groups. MedImmune, Inc. plans to submit these data for priority review by the U.S. Food and Drug Administration (FDA) in the second quarter of 2006, with hopes of having the product available for the 2007 flu season.

Ambrisentan Improves Exercise Capacity in Pivotal Trial[2]

On December 12, 2005, Myogen, Inc. released preliminary results of the ARIES-2 trial, a randomized, double-blind, placebo-controlled pivotal Phase III trial evaluating the investigational medication ambrisentan in pulmonary arterial hypertension (PAH). Ambrisentan is an oral endothelin receptor antagonist, like Tracleer® (bosentan, Actelion Pharmaceuticals US, Inc.). The trial results suggest that patients on ambrisentan therapy have improved exercise capacity and improvements in time to clinical worsening when compared to placebo. A 5 mg dose of ambrisentan given once daily improved the placebo-corrected mean six-minute walk distance by 59.4 meters ($p=0.0002$), while a dose of 2.5 mg of ambrisentan given once daily improved the placebo-corrected mean six-minute walk distance by 32.3 meters ($p=0.0219$). Improvements in time to clinical worsening were seen in both the ambrisentan 5-mg group ($p=0.0076$) and the 2.5-mg group ($p=0.0048$). The most common side effect with ambrisentan therapy was headache, which occurred in 12.7% of patients in the 5-mg group and 7.8% in the 2.5-mg group, compared to 6.2% of patients in the placebo group. Ambrisentan has been granted an orphan designation by the FDA for the treatment of PAH.

Recent Supplemental New Drug Application (sNDA) Approvals[3]*

Product Description	Indication(s)	Approval Date	Route of Administration	Comments
Tamiflu® (oseltamivir) 75 mg, 300 mg/25 mL Roche Pharmaceuticals	The prevention of influenza in children ages 1 year through 12 years	December 22, 2005	Oral - capsules and suspension	This is an expanded indication for an already approved product. The product was previously approved for this indication in adolescents and adults 13 years of age and older.

Recent New Drug Application (NDA) Submissions[3]*

Product Description	Indication(s)	Submission Date	Route of Administration	Comments
arformoterol Sepracor Inc.	Long-term maintenance treatment of chronic obstructive pulmonary disease (COPD)	December 13, 2005	Inhalation - solution	This product is a long-acting bronchodilator. The solution is used with a nebulizer.
Mesavance™ (mesalamine) Shire Pharmaceuticals Group	Induction of clinical and endoscopic remission in patients with active, mild-to-moderate ulcerative colitis	December 22, 2005	Oral	This is a once-daily therapy.

Recent Supplemental New Drug Application (sNDA) Submissions[3]*

Product Description	Indication(s)	Submission Date	Route of Administration	Comments
Aricept® (donepezil) 5 mg, 10 mg Eisai Inc.	Treatment of severe Alzheimer's disease	December 16, 2005	Oral - tablets	This is a re-submission. The sNDA for this indication was originally submitted in August 2005. However, the application was not accepted at that time due to formatting deficiencies. This product is currently approved for the treatment of mild to moderate dementia of the Alzheimer's type.

Recent New Drug Application (NDA) Approvals[3]*

Product Description	Indication(s)	Approval Date	Anticipated Launch Date†	Route of Administration	Comments
iPlex™ (mecasermin) 36 mg/0.6 mL Insmed Incorporated	Treatment of growth failure in children with severe primary IGF-1 deficiency (Primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH	December 12, 2005	Second Quarter 2006	Injection-subcutaneous	This product is dosed once daily.
Nexavar® (sorafenib) 200 mg Bayer Pharmaceuticals Corp./Onyx Pharmaceuticals Inc.	Treatment of patients with advanced renal cell carcinoma	December 20, 2005	The product was expected to launch on December 21, 2005.	Oral - tablets	None

First Generic Product Approvals/Launches[3]*

Generic Product Description	Reference Brand	Dosage Form, Strength(s)	Final Approval Date‡	Anticipated Launch Date†	Comments
azithromycin for injection American Pharmaceutical Partners, Inc.	Zithromax® I.V.	Powder for injection, 500 mg/vial	December 13, 2005	First Quarter 2006	The reference brand is used in the treatment of community-acquired pneumonia and pelvic inflammatory disease.
cefprozil Sandoz, Teva	Cefzil®	Oral suspension, 125 mg/5 mL and 250 mg/5 mL	December 8, 2005	December 2005	The reference brand is used in the treatment of mild to moderate pharyngitis, tonsillitis, otitis media, acute sinusitis, bronchitis, and uncomplicated skin and skin-structure infections.
cefprozil Teva		Tablets, 250 mg and 500 mg	December 6, 2005		
clozapine IVAX Corporation	Clozaril®	Tablets, 200 mg	December 19, 2005	To be announced	This strength is not available as a branded product.
doxycycline monohydrate Lannett Holdings Par Pharmaceutical (authorized generic)	Adoxa®	Tablets, 50 mg and 100 mg	December 8, 2005	December 2005	The reference brand is used in the treatment of many different types of bacterial infections, such as urinary tract infections, respiratory tract infections, and uncomplicated gonorrhea

* 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.

News

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.

FDA Advisory Committee Reviews Merck's RotaTeq® (rotavirus vaccine, live, oral)[4,5]

On December 14, 2005, the FDA's Vaccines and Related Biological Products Advisory Committee met to discuss the safety and efficacy of RotaTeq (Merck & Co., Inc.). RotaTeq is an investigational oral vaccine to prevent rotavirus gastroenteritis. The vaccine targets five strains of rotavirus–G1, G2, G3, G4, and P1. These strains cause a majority of the cases of rotavirus disease worldwide. The vaccine is administered as three doses, with each dose given four to ten weeks apart. The first dose can be administered at 6 weeks to 12 weeks of age.

In the Phase III trial data presented to the committee, six cases of intussuseption (bowel obstruction) were reported in the RotaTeq group, compared to five cases in the placebo group, during a 42-day period. The prevalence of intussuseption was closely monitored in the study because another rotavirus vaccine, RotaShield (Wyeth Laboratories, Inc.), was withdrawn in 1999 due to reports of this adverse event.

The committee voted unanimously that the data support the safety and efficacy of RotaTeq. The committee also recommended that, if RotaTeq is approved by the FDA, Merck should conduct additional post-licensure studies to continue to assess the safety and efficacy of the product.

Rotavirus is the most common cause of severe, dehydrating diarrhea in infants and young children in the United States. In fact, approximately 250,000 emergency room visits and 500,000 clinician visits are caused by rotavirus each year in this country.

FDA Advisory Committee Finds Merck's Zostavax™ (zoster vaccine live) Shingles Vaccine Safe and Effective for Adults Aged 60 Years and Older[6,7]

On December 15, 2005, the FDA's Vaccines and Related Biological Products Advisory Committee met to discuss the efficacy and safety of Zostavax (Merck & Co., Inc.). Zostavax is an investigational vaccine to reduce the risk of shingles, the risk of postherpetic neuralgia, and the total burden of pain and discomfort caused by shingles. The committee unanimously voted that Zostavax is safe and effective for the treatment of shingles in adults aged 60 years and older. However, the committee stated that the data presented were not sufficient to support the use of the vaccine in adults aged 50 to 59 years. Approximately 150 of the 38,000 patients studied were 50 to 59 years of age. In addition, the committee believes there may be a possibility that the efficacy of the vaccine may lessen over time. This may result in exposing patients to shingles and postherpetic neuralgia later in life when the risk of severe pain may be greater. According to Merck, the efficacy of Zostavax does not diminish over time. Instead, there is a decrease in efficacy shortly after the vaccine is administered, but then efficacy stabilizes. A booster dose may be evaluated in future studies of Zostavax. It is estimated that up to one million cases of shingles occur annually in the United States.

Healthcare News

Meta-Analysis Finds No Kidney Benefit for Angiotensin-Converting Enzyme (ACE) Inhibitors or Angiotensin Receptor Blockers (ARBs) When Compared with Other High Blood Pressure Medications[8]

In a meta-analysis of 127 randomized trials, from 1960 to January 2005, the results suggest that the best way to protect the kidneys in patients with diabetes is to lower their blood pressure. The authors found no additional renoprotective (kidney) benefit with ACE inhibitors or ARBs in patients with diabetic nephropathy when compared with other high blood pressure medications. The primary measures studied were the doubling of serum creatinine and end-stage renal disease. Glomerular filtration rate and creatinine amounts were also evaluated.

According to the authors, the kidney benefits of ACE inhibitors and ARBs observed in placebo-controlled trials are probably a result of a reduction in blood pressure caused by the medication. Any additional kidney benefits from these medications beyond lowering blood pressure remain unproven in people with diabetes as well as people with non-diabetic kidney disease. This study was published in the December 10, 2005, issue of *The Lancet*.

Study Links Erectile Dysfunction (ED) to an Increased Risk of Future Cardiovascular Disease[9]

The December 21, 2005, issue of the *Journal of the American Medical Association* includes results of a cohort study of the Prostate Cancer Prevention Trial. It is known that cardiovascular disease and ED may share common causes such as smoking, diabetes, or high blood pressure. For this reason, data from the Prostate Cancer Prevention Trial were analyzed to examine the association of ED and subsequent cardiovascular disease. The sub-study included more than 9,000 men from the Prostate Cancer Prevention Trial and evaluated whether or not ED was associated with heart disease. Of these men, only 47% stated that they had ED at the beginning of the study. Among those men who did not report ED at the beginning of the study, 57% reported having ED after five years. This number increased to 65% after seven years. Men who developed ED during the study had a significantly increased risk of heart attack or chest pain when compared with men who did not develop ED. Upon further investigation, it was observed that developing ED may have the same or greater effect on risk as family history, history of heart attack, cigarette smoking, and high cholesterol with regard to future cardiovascular events.

Based on the findings of this study, the authors concluded that ED may be an indicator of heart disease in some men. Because of this, the authors believe that men who develop ED should be promptly evaluated for risk factors of heart disease.

Clinical Guidelines

Updated Guidelines for the Diagnosis and Management of Sinusitis[10]

The American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma and Immunology have jointly updated their practice parameters for the diagnosis and management of sinusitis (swelling of the sinuses). The new guidelines, which are published in the December issue of the *Journal of Allergy and Clinical Immunology*, offer an updated definition of sinusitis and new recommendations for its diagnosis and management. Other highlights include predisposing factors, the use of antibiotics, tips on when to refer a patient to a specialist, and other diseases associated with sinusitis.

Sinusitis affects approximately 16% of U.S. adults each year and is one of the most commonly diagnosed diseases in this country. This condition accounts for nearly $5.8 billion annually in direct healthcare costs.

Centers for Disease Control and Prevention (CDC) Revises Pertussis (Whooping Cough) Guidelines[11]

In 2004, more than 25,000 cases of pertussis were reported in the United States, the most since 1949. The CDC has recently revised the guidelines for the treatment and postexposure prophylaxis of pertussis. The updated guidelines appear in the December 9, 2005, issue of the *Morbidity and Mortality Weekly Report*.

According to the CDC guidelines, when choosing an antibiotic for treatment or prophylaxis of pertussis, the healthcare provider should consider the effectiveness of the medication as well as its safety, tolerability, ease of adherence to the medication regimen, and cost. For the treatment of pertussis, the guidelines recommend the use of erythromycin, clarithromycin, and azithromycin in persons one month of age and older. For younger infants, azithromycin is the only medication recommended. Trimethoprim-sulfamethoxazole (TMP-SMZ) may be used as an alternative in infants older than two months of age. Erythromycin, clarithromycin, and azithromycin may also be used to prevent pertussis for close contacts of an infected person, as long as there are no contraindications. The benefits of administering an antibiotic to reduce the risk for pertussis and its complications, however, should be weighed against the possible side effects of the medication.

The guidelines also note that the FDA has not approved erythromycin, clarithromycin, and azithromycin for use in infants younger than six months, and the safety and efficacy data regarding the use of azithromycin and clarithromycin in this age group are limited.

The CDC developed these guidelines in consultation with the American Academy of Pediatrics, the American Academy of Family Physicians, and the Healthcare Infection Control Practices Advisory Committee.

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