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Food and Drug Administration Update: Pediatric Highlights

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Over three dozen new drug products and new formulations of previously marketed products were approved by the Food and Drug Administration (FDA) during 2006 and several additional new drugs have already been approved during the first months of 2007. Although only a few of these new drugs have FDA-approved indications for pediatric patients, many of the others may have a role in the treatment of infants and children. In addition to these approvals, the FDA has made several important changes in the labeling of drugs already on the market to include pediatric indications or add new safety information.¹⁻³ This issue of Pediatric Pharmacotherapy will review several of these changes and their impact on pediatric health care.

New Drug Approvals

A live pentavalent rotavirus vaccine (RotaTeq[®]) was approved on February 3, 2006 for the prevention of rotavirus caused by serotypes G1, G2, G3, or G4.¹ This vaccine was reviewed in the September issue of the newsletter at: <http://www.healthsystem.virginia.edu/internet/pediatrics/pharma-news/sept2006.pdf>. Also in February, a combination 0.25% miconazole, zinc oxide, and petrolatum barrier ointment (Vusion[™]) was approved for the treatment of diaper dermatitis with proven candidiasis in children 4 weeks of age and older. It is available by prescription in a 30 gram tube.^{1,5}

A methylphenidate transdermal patch (Daytrana[™]) was approved on April 10, 2006 for the management of attention deficit/hyperactivity disorder (ADHD) in children between 6 to 12 years of age.¹ The clear patch is designed to be worn on the hip and is available in 10, 15, 20, and 30 mg strengths. It should be applied daily and may be left in place for up to 9 hours. The patch provides symptom control for up to 3 hours after removal.^{6,7}

Ibuprofen lysine (Neoprofen[®]) was approved on April 13, 2006 for the treatment of patent ductus arteriosus in preterm infants.¹ In clinical trials, ibuprofen demonstrated a similar rate of ductal

closure as indomethacin, but may have a lower incidence of adverse renal effects.⁸

On April 28, 2006, alglucosidase alfa (Myozyme[®]) was approved for the treatment of Pompe's disease (glycogen storage disease type II).^{1,9} Alglucosidase alfa, a recombinant form of human alpha-glucosidase (GAA), binds to mannose-6-phosphate receptors on cell surfaces, is internalized and then transported into lysosomes, where it cleaves glycogen.⁹ Patients receive a 20 mg/kg dose given every 2 weeks as an infusion. Premarketing clinical trials in patients 1 month to 3.5 years of age demonstrated less need for invasive ventilatory support and improved survival with treatment, compared to historical controls. Administration of alglucosidase alfa must be closely monitored. Approximately 14% of patients in clinical trials or compassionate use programs have developed infusion reactions. These reactions may include severe hypersensitivity reactions, anaphylaxis, or acute cardiorespiratory failure.^{9,10}

Human papillomavirus vaccine (Gardasil[®]) was approved on June 8, 2006 for the prevention of HPV types 6, 11, 16, and 18.¹ It is indicated for use in females between 9 and 26 years of age. More information on this vaccine is available in the November 2006 issue of the newsletter at: <http://www.healthsystem.virginia.edu/internet/pediatrics/pharma-news/nov2006.pdf>.

A new combination product for asthma, an inhaler containing budesonide and formoterol fumarate dihydrate (Symbicort[®]), was approved in July 2006.¹ This product offers another alternative for simultaneous administration of a corticosteroid and a long-acting selective beta₂-agonist. It is currently approved for the long-term maintenance treatment of asthma in patients 12 years of age and older.¹¹ Safety and pharmacokinetic data have been evaluated in children 6-11 years of age, but effectiveness has not yet been established in this age group. The inhaler is available in two strengths: Symbicort[®] 80/4.5 (budesonide 80 mcg/formoterol 4.5 mcg)

and Symbicort[®] 160/4.5 (budesonide 160 mcg/formoterol 4.5 mcg). The recommended dose is 2 inhalations twice daily.

Idursulfase (Elapraxe[™]) was approved by the FDA on July 24, 2006 for the treatment of Hunter Syndrome (mucopolysaccharidosis II).^{1,12} Idursulfase is a recombinant form of human iduronate-2-sulfatase, a lysosomal enzyme which cleaves the 2-O-sulfate esters of terminal iduronate sulfate residues from glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate. Idursulfase is taken up into cellular lysosomes, allowing catabolism of accumulated GAG. The efficacy of idursulfase was evaluated in a 53-week randomized, double-blind, placebo-controlled study of 96 patients with Hunter syndrome (ages 5-31 years).¹³ Patients were randomized to receive idursulfase 0.5 mg/kg IV every week, every other week, or placebo. The composite end-point, improvement in forced vital capacity and distance in a 6-minute walk test, differed significantly between the three groups, with the greatest difference between placebo and weekly treatment (p=0.00049). As a result of this trial, idursulfase is recommended to be administered weekly as an infusion. Patients receiving this therapy require close monitoring. Infusion reactions have been reported in 15% of patients during clinical trials, with 0.2% of patients experiencing significant hypersensitivity reactions.¹²

A new formulation of desonide (Verdeso[™]) was approved in September 2006 for the treatment of mild to moderate atopic dermatitis in patients 3 months of age and older.¹ The product contains 0.05% desonide, a low-potency corticosteroid, in a petrolatum-based emulsion aerosol foam. It may be applied twice daily for up to 4 consecutive weeks.¹⁴

Ciclesonide nasal spray (Omnaris[®]) was approved on October 23, 2006 for adults and children over 12 years of age for the treatment of nasal symptoms associated with seasonal allergies.¹ This product is a non-halogenated glucocorticoid ester which acts as a prodrug and may minimize systemic adverse effects. In a double-blind, placebo-controlled study of 327 adolescents and adults, ciclesonide significantly improved both physician and patient-assessed symptom scores.¹⁵

On February 27, 2007, a new product for ADHD, lisdexamfetamine (Vyvanse[®]), was approved. This inactive pro-drug of dexamphetamine is bonded to L-lysine, limiting its abuse potential. It is, however, still classified as a Schedule II controlled substance. In an open-label study of

lisdexamfetamine in children 6-12 years of age with ADHD, 95% demonstrated improvement in Clinical Global Impressions-Improvement scores. It will be available in three strengths (30, 50, and 70 mg) for once daily dosing.^{1,16}

New Indications

Several drugs received approval from the FDA to include information on use in children over the past year.^{1,2,17} In March 2006, the indications for zanamivir (Relenza[®]), an inhaled antiviral agent for the prevention of influenza, were amended to include use in children 5 years of age or older.

In May 2006, esomeprazole (Nexium[®]) received an additional indication for the short-term treatment of gastroesophageal reflux disease in children 12 to 17 years of age. Fluticasone propionate (Flovent[®] HFA), a glucocorticoid inhaler, also received a pediatric indication, extending use to children as young as 4 years of age. Infliximab (Remicade[®]) was approved on May 19, 2006 for the treatment of children with moderate to severe Crohn's disease refractory to other therapies.

The indications for lamotrigine (Lamictal[®]) were amended to include treatment of primary tonic-clonic seizures in patients 2 years of age and older in September 2006. Pediatric labeling was also added in September for levobetaxolol (Betaxon[®]), used in the treatment of elevated intraocular pressure, and imatinib mesylate (Gleevec[®]), for use in patients greater than 2 years of age with Philadelphia chromosome positive chronic myeloid leukemia unresponsive to other treatments.

In October 2006, risperidone (Risperdal[®]) received an additional indication for the treatment of irritability associated with autistic disorder, including symptoms of aggression, deliberate self-injuriousness, temper tantrums, and quickly changing moods, in children and adolescents between 5 and 16 years of age.

A pediatric indication for balsalazide disodium (Colazal[®]) was approved by the FDA on December 20, 2006. Balsalazide, a prodrug that delivers 5-aminosalicylic acid directly to the colon, is now approved for the treatment of mildly to moderately active ulcerative colitis in children between 5 and 17 years of age. Also in December, celecoxib (Celebrex[®]) received an extension of its indications to include treatment of juvenile rheumatoid arthritis in patients 2 years of age and older. Data from the pediatric studies establishing the efficacy and safety of these drugs in children are available on the FDA

Center for Drug Evaluation and Research (CDER) website.¹⁸

Rejected Application

In August 2006, Cephalon received a non-approvable letter from the FDA in response to their request for approval of a new modafinil product (Sparlon[®]) for the treatment of ADHD. Modafinil, as Provigil[®], is approved for the treatment of narcolepsy and sleep apnea in adults. The FDA advisory panel recommended not to approve the new product because of a possible case of Stevens Johnson syndrome in a child enrolled in a clinical trial of 933 children with ADHD.¹

New Dosage Formulations

Several new pediatric dosage formulations were approved in the past year. A new formulation of prednisolone, oral disintegrating tablets (Orapred ODT[™]), was approved by the FDA in June 2006. The disintegrating tablets are grape-flavored and come in 10, 15, and 30 mg strengths. A chewable 10 mg tablet formulation of loratadine (Children's Claritin[®] Grape Chewables) was approved on August 29, 2006 for the relief of allergic rhinitis in children 2 years of age and older. A 6 mg/mL oral suspension formulation of fexofenadine (Allegra[®]) was approved in October 2006 for the treatment of seasonal allergy symptoms in children 2 to 11 years of age and chronic idiopathic urticaria in children 6 months to 11 years of age.¹

Potential New Drug Approvals for 2007

A number of new drug approvals are expected in 2007, including several agents targeted at pediatric patients. Shire Pharmaceuticals has filed a new drug application for an extended-release formulation of guanfacine (Connexyn[®]) for the treatment of ADHD in children 6 to 17 years of age. Guanfacine is a selective alpha₂-agonist similar to clonidine and has been used off-label for the treatment of ADHD and oppositional defiant disorder for many years. This new product will be dosed once daily and will be available in 1, 2, 2.5, 3, 3.5, and 4 mg strengths. The manufacturer has conducted two placebo-controlled studies in children demonstrating significant improvement in ADHD Rating Scale-IV scores.¹⁹

Cangene's recombinant growth factor (Accretropin[®]) is pending approval for the treatment of growth failure in patients with Turner Syndrome. A synthetic surfactant, lucinactant (Surfaxin[®]), is also under review. Other drugs awaiting approval in adults that may benefit pediatric patients, include desvenlafaxine

(an antidepressant), armodafinil (for treatment of narcolepsy), etoricoxib (a COX-2 inhibitor), levocetirizine (an antihistamine), telavancin and doripenem (antibiotics), ambrisentan and sitaxsentan (for treatment of pulmonary hypertension), another topical lidocaine preparation, a new smallpox vaccine, and a recombinant human thrombin product.²

Recent Safety Warnings

The FDA has released several significant labeling changes and safety alerts that may affect pediatric prescribers.³ A safety advisory was issued on March 30, 2006 for diazepam rectal gel (Diastat[®] AcuDial[™]) notifying health care providers and patients of the risk for cracks at the base of the plastic applicator tip. For more information on inspecting the applicators, refer to the product website at www.diastat.com.

The FDA released a safety alert for promethazine (Phenergan[®] and others) on April 25, 2006 regarding the risk for respiratory depression in children 2 years of age or less. The drug is considered contraindicated in this patient population. Although this information has been released previously, new reports of patient deaths prompted this additional warning.

On August 21, 2006, a boxed warning was added to dextroamphetamine (Dexedrine[®] and others) to alert prescribers to the risk for sudden death in patients with structural cardiac abnormalities or other cardiac problems. Atomoxetine (Strattera[®]) received a boxed warning on October 19, 2006 to highlight the risk for suicidal ideation in children and adolescents. This warning, previously added to all antidepressants, was added because atomoxetine has a similar mechanism of action as the antidepressants (i.e., Norepinephrine transport blockade). Last month, the FDA asked manufacturers of all ADHD treatments, including dextroamphetamine, methylphenidate, dexamethylphenidate, and atomoxetine, to incorporate warning information on both adverse psychiatric and cardiac effects into their labeling and patient information.

Methadone (Dolophine[®] and others) was given a new black box warning on November 27, 2006 highlighting the risk for life-threatening respiratory depression and cardiac arrhythmias. The new labeling is intended to call attention to the risks for dosing errors, opioid conversions, and drug interactions, including those that increase the risk for Torsades de Pointes.

On February 21, 2007, the FDA announced a new black box warning for omalizumab (Xolair[®]) to highlight the risk for anaphylaxis.

The FDA has received information on 48 cases since the release of the drug, including several cases with a delayed onset. Health care providers are advised to monitor patients for a minimum of 2 hours after the administration of omalizumab.

Summary

A number of new drugs were approved by the FDA during the past year that may be of benefit to children. In addition, several drugs received additional indications for use in pediatric patients. While these changes mark the continued growth in available therapies for children, there have also been several important new safety warnings affecting pediatric medications. Health care providers are encouraged to keep up to date with these changes through the FDA websites.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 2/23/07:

1. Decitabine (Dacogen[™]) was added to the Inpatient Formulary for the treatment of patients with myelodysplastic syndromes who have failed therapy with azacitidine.
2. The restrictions on bevacizumab (Avastin[™]) were amended to include use in combination with chemotherapy for metastatic breast cancer and recurrent ovarian cancer.
3. Panitumumab (Vectibix[®]) was added for treatment of refractory EGFR-expressing, metastatic colorectal cancer.
4. The restriction on cetuximab (Erbix[™]) was amended to include use in head and neck cancer.
5. The restriction on trastuzumab (Herceptin[®]) was revised to limit it to patients with HER2-neu positive cancer.
6. Restrictions were deleted for liposomal doxorubicin, imatinib, irinotecan, and oxaliplatin.
7. Etonogestrel (Implanon[™]) was added to the Outpatient Formulary.

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