

PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the
University of Virginia Children's Hospital

Volume 16 Number 2

February 2010

New Drug Approvals and Safety Warnings Affecting Children Marcia L. Buck, Pharm.D., FCCP, FPPAG

More than sixty new drugs or drug formulations were approved by the Food and Drug Administration (FDA) during the past year. Among them were several agents targeted at pediatric disease states. Others not currently approved for pediatric use may still have a role in the off-label treatment of children with serious or refractory illnesses. During the last year, the FDA also made several important labeling changes for drugs already on the market to include pediatric indications or add new safety data. This issue of *Pediatric Pharmacotherapy* will review these new drugs and labeling changes and their potential impact on pediatric health care.

New Drug and Drug Formulation Approvals

Several hematologic products were approved in the past year.¹ On January 16th, fibrinogen concentrate (RiaSTAP[®]), a lyophilized form of human fibrinogen, was approved for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency. On February 6th, recombinant antithrombin (ATryn[®]) was approved for the prevention of thromboembolic events in patients with hereditary antithrombin deficiency.

On April 7th, Coartem[®] (a combination of artemether and lumefantrine) was approved for the treatment of malaria. This combination has been shown to be as effective as standard therapies in children and is well tolerated.² Also in April, a 5% benzyl alcohol-based lotion (Ulesfia Lotion[®]) was approved for the treatment of lice. This product prevents lice from closing their spiracles, killing them via asphyxiation.

A new tumor necrosis factor-alpha (TNF-alpha) blocking agent, golimumab (Simponi[®]), was approved on April 24th as a once-monthly treatment for rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Certolizumab pegol (Cimzia[®]), approved in 2008 for Crohn's disease, received an additional indication on May 13th for rheumatoid arthritis.

A new second generation (atypical) antipsychotic agent, iloperidone (Fanapt[®]) was approved for the treatment of adults with schizophrenia on May 6th. A sustained release preparation of paliperidone (Invega[®]) was approved on August 3rd for schizophrenia. It received an additional indication for the treatment of schizoaffective disorder. Another atypical antipsychotic, asenapine (Saphris[®]) was approved on August 13th for adults.

In May, tadalafil (Adcirca[®]) was approved for use in the treatment of adults with pulmonary hypertension. This agent has been used off-label for several years as a once-daily alternative to sildenafil. In July, an inhaled formulation of treprostinil (Tyvaso[®]), a prostacyclin antagonist also used in the treatment of pulmonary hypertension, was approved; and in November, an injectable form of sildenafil was approved.

An intravenous formulation of ibuprofen (Caldolor[®]) was approved on June 11th for the management of pain or fever. While currently approved only for adults, a pediatric multicenter, randomized, open-label, active-comparator trial will soon begin patient enrollment which may lead to a pediatric indication.

Canakinumab (Ilaris[®]), a human monoclonal antibody to interleukin-1 β , was approved on June 17th for the treatment of adults and children over 4 years of age with cryopyrin-associated periodic syndrome (CAPS).³ CAPS disorders are inherited in an autosomal dominant pattern and result in fever, rash, arthralgia, myalgias, fatigue, and conjunctivitis. Canakinumab is administered as a 2 mg/kg dose (up to 150 mg) given subcutaneously every 8 weeks.

On June 30th, ferumoxytol (Feraheme[®]) injection was approved for the treatment of iron deficiency anemia in adults with chronic kidney disease. Unlike other IV iron products, ferumoxytol can be administered IV push and does not require prophylactic medications or a test dose. Ferumoxytol has also been found to be a useful

tool in imaging studies, and pediatric trials with this product are currently underway.

In July, dronedarone (Multaq®), a benzofuran amiodarone derivative, was approved for the management of adults with atrial fibrillation or flutter. This agent has lower tissue accumulation and a shorter half-life than amiodarone, and lacks the iodine moieties which cause amiodarone's adverse effects on thyroid function. Dronedarone, however, has a much higher incidence of nausea, vomiting, and diarrhea. Prasugrel (Effient®), an oral antiplatelet agent similar to clopidogrel, was also approved that month.

Vigabatrin (Sabril®) was approved by the FDA on August 21st for the treatment of infantile spasms and refractory complex partial seizures.⁴ This agent has been available in Europe and Canada for several years, but has just now come to market in the United States. The risk for blindness associated with vigabatrin must be carefully considered prior to instituting therapy.

While not yet studied in children, telavancin (Vibativ®) is expected to become a valuable agent in the treatment of Gram positive bacterial infections, including methicillin-resistant *Staphylococcus aureus* strains. It was approved on September 11th for once daily IV administration in adults. Studies in animals have revealed teratogenic effects; as a result, telavancin is contraindicated during pregnancy.

Beriner®t, a human plasma-derived C1 esterase inhibitor, was approved on October 9th for the treatment of acute abdominal or facial attacks of hereditary angioedema in adolescents and adults. On December 1st, ecallantide (Kalbitor®) injection, a plasma kallikrein inhibitor, was also approved for acute attacks of hereditary angioedema.

A second human papillomavirus vaccine, Cervarix® (HPV bivalent types 16 and 18 recombinant vaccine) was approved on October 16th. It is indicated for the prevention of cervical pre-cancers and cancer associated with HPV 16 and 18 in females 10-25 years of age.

On November 13th, tranexamic acid (Lysteda®), an antifibrinolytic, was approved for menorrhagia. On December 4th, von Willebrand factor/coagulation factor VIII complex, human (Wilate®) was approved for treatment of spontaneous and trauma-induced bleeding in patients with severe von Willebrand disease.

New Pediatric Indications and Formulations

Over a dozen drugs received additional pediatric indications during the past year as a result of the Pediatric Exclusivity program and the Best Pharmaceuticals for Children Act (BPCA).⁵ Since 1998, these programs have provided incentives for manufacturers to conduct pediatric clinical trials and have played a major role in the increase in drugs with pediatric indications.

Escitalopram (Lexapro®) was approved by the FDA on March 19th for the treatment of major depressive disorder in adolescents between 12 and 17 years of age.⁶ Besides fluoxetine, escitalopram is the only other selective serotonin receptor uptake inhibitor (SSRI) approved for the treatment of major depressive disorder in pediatric patients.

On April 30th, almotriptan (Axert®) was approved for the acute treatment of pediatric migraine in adolescents between 12 and 17 years of age. This drug is the first of the serotonin receptor agonists, the "triptans," to be approved for use in pediatric patients.⁷ The approval was based on the results of a multicenter, randomized, double-blind, placebo-controlled trial in adolescents which demonstrated significant benefit, as well as the known efficacy and safety of the drug in adult clinical trials.

The indications for three antihistamines were extended to include younger children. On August 21st, the indication for levocetirizine (Xyzal®) was expanded to include treatment of seasonal allergic rhinitis in children 2 years of age and older. The indication for treatment of perennial allergic rhinitis and chronic idiopathic urticaria were expanded to include children 6 months of age and older. Two weeks later, the indication for azelastine nasal spray (Astepro®) was expanded to include the treatment of seasonal and perennial allergic rhinitis in children 12 years of age and older. The indication for bepotastine besilate (Bepreve®) was extended on September 8th to include children 2-10 years of age with ocular itching associated with allergic conjunctivitis.

On August 28th, valganciclovir (Valcyte®) received an indication for the prevention of cytomegalovirus (CMV) disease in pediatric heart and kidney transplant patients over 4 months of age.⁸ Valganciclovir was already being used for CMV prophylaxis by many pediatric transplant centers. In conjunction with their petition for pediatric approval, the manufacturer also developed a 50 mg/mL oral

suspension for use in children. The package labeling for this product includes new dosing recommendations based on a recent study that found dosing by body surface area produced more reliable serum concentrations than weight-based dosing.⁹

An extended release formulation of guanfacine (Intuniv[®]) was approved on September 2nd for the treatment of ADHD. This product, described in the April 2008 issue of *Pediatric Pharmacotherapy*, is the first alpha-adrenergic agonist to be specifically approved by the FDA for use in children with ADHD.¹⁰

In October, both colesevelam and rosuvastatin received an indication for the treatment of heterozygous familial hypercholesterolemia in children 10 years of age and older. Colesevelam (Welchol[®]), a bile acid sequestrant, was approved on October 2nd. Rosuvastatin (Crestor[®]), an HMG-CoA reductase inhibitor or “statin,” received the same pediatric indication on October 19th.

On October 16th, the indication for HPV vaccine (Gardasil[®]) was extended to boys and men from 6 to 26 years of age. The Advisory Committee on Immunization Practices of the Centers for Disease Control has not recommended inclusion of this vaccine into the childhood immunization series for males at this time.

Three atypical antipsychotics received pediatric labeling during the past year. On November 19th, aripiprazole (Abilify[®]) was approved for the treatment of irritability associated with autistic disorder in adolescents. In December, both olanzapine (Zyprexa[®]) and quetiapine (Seroquel[®]) received additional indications for the treatment of bipolar disease and schizophrenia in children. Quetiapine was approved for the treatment of schizophrenia in children 13-17 years of age and bipolar mania in children 10-17 years of age. Olanzapine was approved for manic or mixed episodes of bipolar I disorder and schizophrenia in children 13-17 years of age.

Recent Safety Warnings

Several significant medication safety alerts and labeling changes have been made by the FDA over the past year. The following section highlights some of these changes. More MedWatch information can be found at www.fda.gov/Safety/MedWatch/SafetyInformation/Safety-RelatedDrugLabelingChanges/default.htm.¹¹

In January, the FDA added a warning label to all SSRIs, venlafaxine, desvenlafaxine, and duloxetine to call attention to the risk for neuroleptic malignant syndrome or serotonin syndrome with these agents. The warning came after an increased number of these cases were submitted to the FDA and published in the medical literature.

The following month, the labeling for all heparin products was amended to include several new warnings, including the risk for neonatal dosing errors and the risk for heparin-induced thrombocytopenia. This revision in labeling was made after repeated reports of medication errors with heparin products, some leading to significant morbidity or mortality. The Joint Commission has also issued a Sentinel Event Alert on safe use of anticoagulants.¹²

A labeling change was made to ceftriaxone in March contraindicating its use in neonates receiving calcium-containing products. This warning was based on a small number of patient deaths in a crystalline precipitation was found in the lungs and kidneys at autopsy.

In April, the labeling for all antiepileptics was amended to include warnings regarding suicidal ideation and potential teratogenic effects. Prescribers caring for women who become pregnant while taking an antiepileptic are asked to encourage them to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Patients can enroll by calling 1-888-233-2334 or going to www.aedpregnancyregistry.org/. This voluntary registry, established in 1997, is supported by Massachusetts General Hospital and contains information from over 6,500 women.

Several important labeling changes were made in June, including the addition of information on tardive dyskinesia to the prescribing information for metoclopramide. Based on studies showing a 20% incidence in patients treated for more than 12 weeks, the FDA recommends limiting therapy to no longer than 12 weeks unless the benefits clearly outweigh the risk. A warning for severe liver dysfunction was added to the adverse effects associated with atomoxetine, based on reports of serum transaminases up to 20 times the upper limit of normal and elevated bilirubin levels. The risk for red cell aplasia was added to the labeling for mycophenolate mofetil and mycophenolic acid, as well as information on drug interactions with ciprofloxacin and amoxicillin/clavulanic acid.

In July, a warning was added to HPV vaccine (Gardasil®) regarding syncope or convulsive syncope after vaccine administration. It is recommended that patients be observed, preferably while sitting or lying down, for at least 15 minutes after receiving the vaccine. The following month, a precaution was added to all antipsychotics regarding the potential for leukopenia, neutropenia, and agranulocytosis.

The labeling for mycophenolate was amended again in October to add a warning regarding reports of progressive multifocal leukoencephalopathy (PML) and BK virus-associated nephropathy (BKVAN) in patients receiving immunosuppressants, including mycophenolate. Also that month, the FDA added a warning to desipramine for the risk of cardiac arrhythmias and to granisetron and dolasetron for QT prolongation. Ondansetron already carries this same warning.

In November, the FDA added black box warnings for all TNF-alpha blockers regarding the risk for lymphoma and other malignancies in children and adolescents with autoimmune diseases. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma, while the other cases included rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in pediatric patients. The average length of therapy at the time of diagnosis of the malignancy was 30 months, with a range of 1 to 84 months. Most patients were receiving multiple immunosuppressants.

Summary

A wide variety of new drugs were approved by the FDA during the past year that may be of benefit to children. In addition, many drugs received pediatric indications or were marketed in new pediatric dosage formulations. These changes demonstrate continued growth in the number of pediatric clinical trials being conducted and the value of initiatives to stimulate pediatric drug research. There were also several important new safety warnings issued during the past year. Health care providers are encouraged to use the FDA's website to stay current with these alerts.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 1/22/10:

1. Tolvaptan (Samsca™) was added to the Formulary, with restriction to Cardiology and Nephrology, for refractory hyponatremia.
2. Ferumoxytol (Feraheme®) was added for treatment of iron deficiency anemia in adults with chronic kidney disease who are not dialysis-dependent.
3. Granisetron (generic), a 5-HT₃ receptor antagonist, was added to the Formulary for the prevention of nausea and emesis.
4. Lanreotide (Somatuline®) Depot was deleted from the Formulary, and a request for torsemide was rejected.

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