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New Drug and Drug Formulation Approvals for Children

Marcia L. Buck, Pharm.D., FCCP, FPPAG

A number of new drugs and drug formulations have been approved by the Food and Drug Administration (FDA) during the first half of 2014, including several for use in children. The FDA has also made labeling changes for several drugs already on the market to include pediatric indications.[1,2]

New Drug Approvals

Elosulfase alfa

On February 14, 2014, the FDA approved elosulfase alfa (Vimizim™) for the treatment of mucopolysaccharidosis type IVA.[3] This rare genetic lysosome storage disease, also referred to as Morquio A syndrome, is caused by a deficiency of N-acetylgalactosamine-6-sulfate sulfatase. Elosulfase alfa was studied in a 24-week randomized, double-blind, placebo controlled trial prior to approval.[4] A total of 176 patients, 5-57 years of age were randomized to receive a 2 mg/kg infusion of elosulfase alfa weekly, every other week, or placebo. Weekly treatment resulted in significant improvements in mobility compared to placebo. The mean effect on 6 minute walk test at 24 weeks was 22.5 meters (95% CI 4.0, 40.5, p = 0.017). Of the original 176 patients, 173 chose to continue treatment in an open-label extension study. Results of this study have shown no evidence of a reduction in efficacy over time.

The most common adverse effects reported during the original trial included fever, headache, chills, fatigue, nausea, vomiting, and abdominal pain. There have also been reports of anaphylactic reactions during infusions. Prescribing information for the drug contains a black box warning regarding this risk. Elosulfase alfa was the first drug to be given a Rare Pediatric Disease Priority Review Voucher, a new FDA designation designed to stimulate the development of new treatments for rare diseases. Healthcare providers and families can obtain more information about elosulfase alfa from BioMarin Pharmaceuticals by calling 1-855-MORQUIO (1-855-667-7846) or sending an email to bpps@bmrn.com.

Metreleptin

Metreleptin (Myalept™), a recombinant analogue of leptin, was approved on February 24, 2014, with an orphan product designation to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystropy.[5] This condition may lead to severe insulin resistance and the development of treatment-resistant diabetes mellitus and hypertriglyceridemia. Metreleptin was studied in an open-label study of 55 patients prior to approval.[6] The median patient age was 25 years (range 7-68 years). Median duration of treatment was 2.5 years. The mean reduction in $HgbA_{1c}$ was 2.1 $\pm$ 0.5%, with a reduction in fasting triglycerides of 35.4 $\pm$ 13.7%.

In patients weighing 40 kg or less, metreleptin should be initiated at a dose of 0.06 mg/kg given once daily by subcutaneous injection. In males over 40 kg, treatment should be initiated with a daily dose of 2.5 mg and in females over 40 kg, a dose of 5 mg should be used. The dose may be titrated up to a maximum of 0.13 mg/kg/day in patients weighing 40 kg or less and 10 mg/day in those over 40 kg. The most common adverse effects in clinical trials were headache, hypoglycemia, and abdominal pain. Prescribers treating infants with metreleptin should be aware that the injection contains benzyl alcohol.

Because of the risk for development of anti-metreleptin antibodies with neutralizing activity to leptin/metreleptin and the risk for serious infection or T-cell lymphoma, metreleptin is only available through the Myalept™ Risk Evaluation and Mitigation Strategy (REMS) Program. The REMS program, in addition to other post-marketing studies, has been required by the FDA to provide a mechanism for assessing immunogenicity and capturing information on potentially rare, but serious adverse effects.

Miltefosine

On March 19, 2014, the FDA approved miltefosine (Impavido®) for the treatment of leishmaniasis in children 12 years of age and older and adults.[7] Miltefosine was approved to treat visceral, cutaneous, and mucosal leishmaniasis. It is the first drug to be approved by the FDA for cutaneous or mucosal leishmaniasis. Because of the rarity of the infection and the limited number of treatment options available, miltefosine was given a fast track designation and a Tropical Disease Priority Review Voucher. It has also been granted orphan product designation. Miltefosine is available as a 50 mg capsule. The recommended dose for patients weighing 30-44 kg is 50 mg twice daily, and for patients 45 kg or greater, 50 mg three times daily, for 28 days. It is contraindicated in pregnant women due to evidence of teratogenicity and fetal death in animal models. The most common adverse effects reported during four clinical trials included nausea, vomiting, abdominal pain, decreased appetite, diarrhea, headache, dizziness, and elevated serum transaminases and creatinine.

Recombinant Factor IX

A recombinant form of Factor IX, Alprolix™, was approved on March 28, 2014 for the treatment of children and adults with hemophilia B.[8] This formulation offers the advantage of a longer duration of effect, resulting from the linking of the Factor IX molecule to the Fc protein fragment of human IgG. Binding of the Fc portion to neonatal Fc receptors delays lysosomal degradation of immunoglobulins by directing it back into the circulation, and gives recombinant Factor IX a prolonged half-life.

A total of 123 patients, ages 12-71 years, with severe hemophilia B were studied for over a year as part of a multicenter open-label clinical trial to establish the safety and efficacy of this new formulation.[8] Patients were treated on one of three regimens: a fixed-week interval, an individualized interval, or on an as needed basis. In all groups, recombinant Factor IX was effective in reducing bleeding episodes. There were no significant adverse effects associated with the Factor. Pharmacokinetic studies in children under 12 years of age have shown a higher bodyweight-adjusted clearance than that seen in older children and adults. In a study of 29 children, mean elimination half-life was 66.40 hrs in patients 2-5 years, 72.23 hrs in those 6-11 years, and 83.59 hrs in those 12-17 years. For comparison, the mean half-life in a study of adults was 86.52 hrs. This shorter half-life may result in the need to adjust recombinant Factor IX dosing intervals in younger patients.

Sublingual Allergen Extracts

The first sublingual allergen extract tablet, Oralair®, was approved by the FDA on April 2, 2014, for the treatment of grass pollen allergies in patients between 10 and 65 years of age.[9] Oralair® contains a mixture of freeze-dried extracts from five common grasses: Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass. The tablets are available in 100 and 300 IR (index of reactivity). Patients 17 years of age and older should receive one 300 IR tablet. Younger patients should undergo a dose titration with a 100 IR tablet the first day, two 100 IR tablets the second day, and a 300 IR tablet the third day and thereafter.

The first dose for all patients should be administered in the healthcare provider's office or clinic to allow a minimum of 30 minutes of observation and potential treatment of a severe hypersensitivity reaction, including anaphylaxis. If tolerated, further doses may be taken by the patient at home, providing a more convenient alternative to allergy shots. The recommended regimen is one tablet daily, beginning 4 months before the start of grass pollen season and continuing until the end of the season. The manufacturer recommends that patients be trained in the use of an epinephrine auto-injector and the need to seek medical attention if symptoms of hypersensitivity develop. Patients with severe or uncontrolled asthma, cardiac disease, or who require medications known to reduce the efficacy of epinephrine should not be treated with sublingual allergen extracts.

Oralair® was studied in six clinical trials in over 1,000 adults throughout the United States and Europe.[9] In addition, 278 children (ages 5-17 years) were enrolled in a placebo-controlled study. The mean daily total symptom score was significantly lower in the treatment group than in the controls (2.52 versus 3.13) with a relative difference of -30.6% (95% CI -47.0%, -14.1%), as was the mean daily rescue medication score (0.46 versus 0.65) with a relative difference of -29.5% (95% CI -50.9%, -8.0%). A subset of 154 children was included in a safety analysis. The most commonly reported adverse effects in children were similar to those in adults: upper respiratory infections, tonsillitis, worsening asthma, dysphonia, pruritus, and atopic dermatitis. Approximately 1% of patients experienced a severe adverse effect, including hypersensitivity reactions and laryngeal edema.

On April 14, 2014 Merck announced the FDA approval of their sublingual Timothy grass pollen allergen extract tablet, Grastek®.[10] This product is approved for a wider patient population, from 5 to 65 years of age. Grastek® should be started 12 weeks prior to the onset of

grass pollen season and continue to the end of the season. A second sublingual allergen extract tablet from Merck was recently approved adults 18 years of age and older with ragweed allergy.[11] Short ragweed allergen pollen extract (Ragwitek™) was approved by the FDA on April 17, 2014. As with Grastek®, treatment should begin 12 weeks before the onset of ragweed pollen season and continue throughout the season. Like Oralair®, the first dose of either Grastek® or Ragwitek™ should be given in the office or clinic to allow observation for a minimum of 30 minutes. Both products carry the same black box warning and precautions as Oralair®.

New Product Formulations

Extended-Release Topiramate Capsules

In August 2013, the FDA approved the first extended-release topiramate capsule, Trokendi XR™.[12] This once daily product is available in 25 mg, 50 mg, 100 mg, and 200 mg strengths. It is approved for use as monotherapy in patients 10 years of age and older with partial-onset seizures or primary generalized tonic-clonic seizures and as adjunctive therapy in patients 6 years of age and older with either partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome. A second extended-release topiramate capsule, Qudexy™ XR, was approved on March 12, 2014.[13] Like Trokendi XR™, it is approved for use as monotherapy in patients 10 years of age and older with partial-onset seizures or primary generalized tonic-clonic seizures, but the approval for use as adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut syndrome includes patients as young as 2 years of age.

Qudexy™ XR was studied in a global randomized, double-blind, placebo-controlled phase 3 trial (PREVAIL) conducted in 249 patients.[13] After 3 weeks of dose titration and 8 weeks of maintenance therapy, there was a significant decrease in seizure frequency with treatment (39.5% versus 21.7%, $p < 0.001$). The capsules will be available in 25 mg, 50 mg, 100 mg, 150 mg, and 200 mg strengths. Unlike Trokendi XR™, the Qudexy™ XR capsules are labeled with information stating that they can be swallowed whole or opened and the contents sprinkled onto a spoonful of a soft food.

Propranolol Oral Solution

A new formulation of propranolol, Hemangeol®, was approved by the FDA on March 17, 2014, for the treatment of infantile hemangiomas.[14] The use of propranolol to treat infantile hemangiomas was first reported in 2008 by Léauté-Labréze and colleagues at Bordeaux Children's Hospital.[15] The response noted by the authors, improvement in all 11 patients treated, quickly led to the adoption of propranolol as a first-line therapy. Subsequent reviews have confirmed its efficacy.[16] Of the 460 infants with proliferating infantile hemangioma enrolled in a randomized double-blind study of Hemangeol®, 60% had complete or nearly complete resolution of their hemangioma after 6 months, compared to only 4% of the controls ($p < 0.0001$).[14]

Hemangeol® solution is approved for use in infants at least 5 weeks of age and weighing more than 2 kg.[14] The recommended starting dose is 0.6 mg/kg given twice daily. After one week, the dose may be increased to 1.1 mg/kg twice daily, and after 2 weeks to 1.7 mg/kg twice daily. Propranolol should be given during or after feeding to avoid hypoglycemia. The manufacturer recommends checking blood pressure and heart rate 2 hours after the initial dose and any dose increase. The most commonly reported adverse effects in clinical trials have been difficulty sleeping, upper respiratory tract infections, vomiting, and diarrhea.

Mercaptopurine Oral Solution

On April 28, 2014, the FDA approved a new 20 mg/mL oral suspension of mercaptopurine (Purixan™) for the treatment of patients with acute lymphoblastic leukemia.[17] Mercaptopurine has been available in the United States since 1953, but only as a 50 mg tablet. Prior to the availability of this new formulation, use of doses smaller than half a tablet required the preparation of an extemporaneous liquid by a pharmacist. Approval was based on a bioequivalence study conducted with the solution and Purinethol® 50 mg mercaptopurine tablet in adults.

New Pediatric Indications

Topiramate

The FDA extended the approval of topiramate for the treatment of migraines to adolescents 12-17 years of age.[18] It had been approved for migraines in adults in 2004. The approval was based on the results of a placebo-controlled clinical trial of 103 patients 12-17 years of age. There was a significant reduction in the treated patients compared to controls (72% versus 44%).

Omalizumab

The monoclonal antibody omalizumab (Xolair®), first approved for the treatment of severe asthma in 2003, received an indication for the treatment of chronic idiopathic urticaria in patients 12 years of age and older on March 21, 2014.[19] In a randomized, double-blind trial of 2323 patients, omalizumab produced significant improvements

in symptoms in patients who failed to respond to antihistamines.[20]

Ecallantide

On April 4, 2014, the FDA approved an expansion of the indication for ecallantide (Kalbitor®), a peptide inhibitor of plasma kallikrein used to treat acute hereditary angioedema, to patients as young as 12 years of age.[21] Ecallantide is the only subcutaneous therapy available in adolescents. The use of ecallantide in patients 12-15 years of age was extrapolated from clinical trials in adults and pharmacokinetic studies demonstrating similar pharmacokinetic parameters in adolescents and adults.

Summary

A wide variety of new drugs have recently been approved by the FDA that may be of benefit to children. In addition, several drugs received pediatric indications or were marketed in new 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. Health care providers are encouraged to go to www.fda.gov to sign up for email updates or follow the FDA on Facebook or Twitter to be informed of new drugs and labeling changes.

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Formulary Update

The following actions by the Pharmacy and Therapeutics Committee at their May meeting:

1. Gadoterate (Dotarem®) was added to the Formulary.
2. MediHoney and ELTA SilverGel were added to the Formulary as options for wound care.
3. The restriction on apixaban was amended to included vascular medicine for off-labeled use; restrictions to FDA-approved indications for initiation of therapy, patients maintained on therapy prior to admission, and to Hematology for off-labeled use was retained.
4. Lansoprazole delayed-release disintegrating tablets (Prevacid® SoluTab) were deleted from the Formulary due to the addition of lansoprazole oral suspension to Formulary in October 2013.