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New Drug Approvals and Extended Indications for Infants, Children, and Adolescents

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Over the past six months, a number of significant new drugs have been approved by the Food and Drug Administration (FDA). In addition, several drugs already on the market have been granted an indication for use in pediatric patients.

New Drug Product Approvals

Adapalene and Benzoyl Peroxide

Epiduo Forte®, a new product containing adapalene 0.3%, a retinoid, and benzoyl peroxide 2.5% was approved on July 16, 2015 for the treatment of moderate to severe acne in adults and children 12 years of age and older.[1] The efficacy of the new product was demonstrated in a phase 3 multicenter randomized, double-blind trial comparing it to the gel vehicle without the two active ingredients and a combination product containing adapalene 0.1% and benzoyl peroxide 2.5%.[2] Patients in the adapalene and benzoyl peroxide groups had significantly greater reductions in skin lesion count at 12 weeks, with a mean absolute reduction of 68.7% versus 39.2% in the controls. Many patients experienced improvement after the first week. Fifty percent of the patients receiving active treatment rated themselves as having a marked improvement, compared to only 11% of the controls. Adverse effects were mild, consisting of skin irritation in 4% of patients and eczema, dermatitis, or a burning sensation in 1%. Adapalene and benzoyl peroxide gel may offer an effective alternative to the long-term use of antibiotics for the treatment of moderate to severe acne.

Amphetamine Extended-Release Suspension

A once-daily amphetamine oral suspension (Dyanavel™ XR) was approved by the FDA on October 19, 2015 for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years of age and older.[3] The product includes both immediate-release and extended-release amphetamine. The extended-release component is coated with an aqueous polymer which slowly releases the drug over time, providing up to 13 hours of symptom control. The safety and efficacy of the product was established in a phase 3 randomized, placebo-controlled trial in 108 children with ADHD.[4] Following a 5-week open-label dose optimization period, patients were randomized to treatment (2.5-10 mg) or placebo for a 1-week period. At the end of the week, scores on the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-Combined rating scale were compared to baseline. The change in scores after treatment demonstrated a statistically significant improvement throughout the day compared to placebo (assessed at 1, 2, 6, 8, 10, 12, and 13 hours post-dose), with a mean change of -8.8 (SE 1.14) in the treated patients and 6.0 (SE 1.19) in the controls. Dyanavel™ XR contains 2.5 mg amphetamine base/mL, equivalent to 4 mg of mixed amphetamine salt, in a bubble-gum flavored suspension. Tris Pharma anticipates having the product available in early 2016.

Asfotase Alfa

On October 23, 2015, the FDA approved the use of asfotase alfa (Strensiq™), a tissue nonspecific alkaline phosphatase enzyme replacement therapy for patients with perinatal, infantile, or juvenile-onset hypophosphatasia (HPP).[5] Affecting approximately one in 100,000 newborns, HPP is a progressive metabolic disease resulting in muscle weakness and defective bone mineralization. Asfotase alfa replaces tissue-nonspecific alkaline phosphatase, improving formation of normal bone. The efficacy and safety of the drug were established in four open-label studies.[6,7] In patients with perinatal or infantile-onset HPP, asfotase alfa improved both overall survival and ventilator-free survival. Ninety-seven percent of patients were alive at one year of age, compared to an anticipated 42% based on historical controls. In studies of patients with juvenile-onset HPP, there were significant improvements in growth and bone mineralization.

Asfotase alfa is administered by injection three or six times per week. The most commonly reported adverse effects in patients enrolled in the open-label studies were injection site reactions, hypersensitivity reactions, lipodystrophy at injection sites, and ectopic calcifications in the eyes or kidneys.[5-7] The drug was granted both Breakthrough Therapy and Orphan Drug designations by the FDA.

Cysteamine Bitartrate Delayed-Release Capsules

A delayed-release form of cysteamine bitartrate (Procysbi®) was approved by the FDA on August 14, 2015 for management of nephropathic cystinosis in adults and children 6 years of age and older.[8,9] Cysteamine bitartrate immediate-release tablets (Cystagon®) were approved by the FDA in 1994. The slower release of drug from the Procysbi capsule allows for twice-daily dosing rather than the every 6-hour dosing required for Cystagon®. The approval of the delayed-release product was based on a randomized cross-over study comparing it to the immediate-release tablets in 43 children and adults. The two products were equally effective in controlling cysteine levels. Cysteamine bitartrate delayed-release was given an Orphan Drug designation by the FDA.

Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Alafenamide

On November 5, 2015, the FDA approved a fixed-dose combination tablet of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide (Genvoya®) for the management of HIV-1 infection in adults and children 12 years of age and older who weigh at least 35 kg.[10,11] This once-daily product may be used in either treatment naïve patients or those who have already been receiving treatment. The combination contains a prodrug of tenofovir that produces higher concentrations within cells with lower serum concentrations, providing effective antiviral activity with fewer adverse effects on renal function and bone mineral density.[12]

Mepolizumab

The FDA approved mepolizumab (Nucala®) for the management of severe asthma in patients 12 years of age and older on November 4, 2015.[13] Mepolizumab is a humanized monoclonal antibody to interleukin-5. It is given by subcutaneous injection every 4 weeks by a health care professional to monitor for hypersensitivity reactions.[14] Mepolizumab was evaluated in three premarketing randomized, double-blind placebo-controlled trials. In the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) study, 576 adolescents and adults were randomized to receive either a 75 mg IV dose or 100 mg subcutaneous dose of mepolizumab or placebo. All patients remained on their current asthma medications. The rate of exacerbations was reduced by 47% in the IV mepolizumab group and 53% in the subcutaneous group as compared to the placebo group ($p < 0.001$ for both comparisons). Emergency room visits or hospitalizations were reduced by 32% and 61% in the two treatment groups, respectively.[15] In the combined results of premarketing studies, a reduction in steroid use of 50% or more was documented in 54% of the treated patients versus 33% of the controls. Twenty-three percent of treated patients achieved a 90-100% reduction in steroid use, compared to only 11% of the controls. The most common adverse effects reported with mepolizumab include headache (19% of patients), injection site reactions (8%), and back pain (5%). Symptoms associated with hypersensitivity reactions have been reported in 1-2% of patients.[14]

Uridine Triacetate

Uridine triacetate was approved on September 4, 2015 for the treatment of patients with hereditary orotic aciduria (HOA).[16] Patients with HOA are unable to synthesize uridine, an essential component of RNA, and are prone to anemia, neutropenia, developmental delays, failure to thrive, and urinary tract obstructions caused by orotic acid crystals in the urinary tract.[17] Uridine triacetate is available in oral granules that can be mixed with food, milk, or infant formula. It is administered once daily. The safety and efficacy of uridine triacetate were evaluated in a 6-week open-label trial in four patients with HOA (3-19 years of age). This study was followed by a 6-month extension phase. At 6-week and 6-month evaluations, treatment resulted in stable hematologic parameters. No adverse effects have been reported with treatment up to 9 months. Uridine triacetate was granted Orphan Drug status by the FDA, as well as a rare pediatric disease priority review voucher.

New Pediatric Indications

Abacavir and Lamivudine

The FDA approval for the combination of abacavir and lamivudine (Epzicom®) was extended on September 17, 2015 to include use in children with HIV-1 infection weighing 25 kg or more.[18] The weight limit is the result of the need for the patient to receive the currently available tablet containing 600 mg abacavir and 300 mg lamivudine. The FDA waived the requirement for pediatric studies in patients weighing less than 25 kg and the development of an oral liquid formulation because of the availability of similar products for that population.

The efficacy and safety of the abacavir and lamivudine combination were evaluated in the

ARROW trial, a 5-year multicenter randomized trial which included 23 children with HIV-1 infection who were treatment-naïve and between the ages of 3 months and 17 years of age.[19] The initial phase consisted of abacavir and lamivudine dosed twice daily according to current World Health Organization recommendations. After 36 weeks, patients could be enrolled in a second phase comparing once-daily and twice-daily dosing of the combination, given along with a third antiretroviral drug, for an additional 96 weeks. A total of 669 of the original 1,206 patients in the ARROW trial were included. The percentage of subjects with an HIV-1 RNA less than 80 copies/mL at week 96 were not significantly different: 70% in the twice-daily dosing group and 67% in the once-daily group. There were no differences in the frequency of adverse effects between the groups. Based on this study and others, once-daily administration of Epzicom® has been approved by the FDA.

Aprepitant

On August 2, 2015, the FDA indication for aprepitant (Emend®) was amended to include adolescents 12 years of age and older and children less than 12 years who weigh at least 30 kg.[20] Aprepitant is an antiemetic that serves as an antagonist at substance P/neurokinin 1 (NK1) receptors. It is used in combination with other antiemetics in the prevention of acute or delayed nausea and vomiting associated with moderately or highly emetogenic chemotherapy. The expanded indication was based on the results of a randomized, double-blind active-comparator study comparing aprepitant and ondansetron to ondansetron alone in 132 children and adolescents. There was a significantly greater percentage of subjects with a complete response (0-24 hours after chemotherapy) in the combination group (34.9%) compared to the group given ondansetron alone (13%). Results were also significant for comparisons of response in the acute and delayed phases when assessed independently.

Atazanavir

The approved age range for atazanavir (Reyataz®) oral powder for suspension was extended by the FDA on September 24, 2015 to include treatment of HIV-1 infection in children 3 months of age or older who weigh at least 5 kg.[21] The age extension was based on two pharmacokinetic, safety, and efficacy studies: PRINCE 1, conducted in children 3 months to 6 years of age, and PRINCE II, conducted in children 3 months to 11 years of age.[22] A total of 155 children were studied. The percentages of antiretroviral-experienced and antiretroviral-naïve patients with HIV-1 RNA counts less than 400 copies/mL at week 48 were 79% and 62%, respectively. The percentages with HIV-1 RNA counts less than 50 copies/mL were 54% and 50%. The median increase in absolute CD4 count at week 48 for the two groups were 215 cells/mm^3 and 133 cells/mm^3, respectively.

Mesalamine Delayed-Release Capsules

On September 9, 2015, the FDA granted an extension of the approval for mesalamine delayed-release 400 mg capsules (Delzicol®) to include children 5 years of age and older.[23,24] The product was previously approved for adults and children 12 years of age and older. Mesalamine, an aminosalicylate, blocks the mucosal production of arachidonic acid metabolites that are increased in patients with chronic ulcerative colitis. The delayed-release form provides effective topical anti-inflammatory activity in the colon. The effectiveness of delayed-release mesalamine was studied in 82 children between 5 and 17 years of age with mild to moderately-active ulcerative colitis. In a 6-week randomized, double-blind, parallel-group study, patients were divided into groups (17-32 kg, 33-53 kg, and 54-90 kg) and randomly assigned to a low-dose (1.2, 2.0, or 2.4 g/day) or high-dose (2.0, 3.6, or 4.8 g/day) regimen. At week 6, 73.2% of patients in the low-dose group and 70.0% in the high-dose group experienced successful treatment. Of those patients, 34.1% in the low-dose group and 42.5% in the high-dose group had a complete resolution of symptoms. Based on the similar degree of benefit between the two dosing strategies, the low-dose regimen was chosen for approval.

Rilpivirine

On August 26, 2015, the FDA extended the approval for rilpivirine (Edurant®) to include HIV-1 treatment-naïve pediatric patients 12 years of age and older who weigh at least 35 kg.[25,26] Rilpivirine is indicated for the treatment of patients with an HIV-1 RNA < 100,000 copies/mL and is given as one 25 mg tablet once daily with a meal. The pharmacokinetics, safety, and efficacy of rilpivirine were evaluated in a 48-week phase 2 open-label trial in 36 treatment-naïve children with HIV-1 infection between 12 and 18 years of age. In patients with an HIV-1 RNA $\geq$ 100,000 copies/mL at baseline, 50% had level < 50 copies/mL at week 48. Of the patients with a baseline HIV-1 RNA < 100,000 copies/mL, 79% had an HIV-1 RNA < 50 copies/mL. The mean increase in CD4 count from baseline was 201.2 cells/mm^3.

Tiotropium

The FDA extended approval of tiotropium (Spiriva® Respimat®) to include the treatment of asthma in adults and children 12 years of age and older on September 15, 2015.[27,28] Tiotropium had previously been approved only as a maintenance

treatment for patients with chronic obstructive pulmonary disease. Efficacy and safety data for its use in asthma was obtained from 12 clinical trials of nearly 5,000 adolescents and adults with asthma. In placebo-controlled trials, the addition of tiotropium to standard therapy significantly improved lung function and reduced asthma exacerbations. The recommended dose is 2.5 mcg (2 puffs) once daily.

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