



News for Pediatric Healthcare Providers from the Food and Drug Administration

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The Food and Drug Administration (FDA) approved 48 novel drugs and biologics in 2017. Several of these drug and drug product approvals are of benefit to the pediatric patient population. This issue of the newsletter will review these new treatment options, as well as previously approved medications given new pediatric indications and new drugs currently under FDA review.

New Drug and Drug Product Approvals

Avelumab

Avelumab (Bavencio®), an anti-PD-L1 IgG1 monoclonal antibody, has been approved for the treatment of metastatic Merkel cell carcinoma in adults and children more than 12 years of age. Approval was based on the JAVELIN Merkel 200 trial, a multicenter open-label, non-comparator study in 88 adults showing an overall response rate of 33%, with a complete response in 11% and a partial response in 22%.¹

Benralizumab

An interleukin-5 receptor monoclonal antibody, benralizumab (Fasenra™) has been approved for the treatment of severe eosinophilic asthma in adults and pediatric patients 12 years of age and older.² By binding at the IL-5 receptor on the surface of eosinophils and basophils, it produces antibody-dependent cell elimination within 24 hours of administration. The 30 mg dose is administered subcutaneously once every 4 weeks for the first three doses, and then once every 8 weeks thereafter. Three phase 3 studies supported the drug's approval, demonstrating up to a 51% reduction in asthma exacerbation rates compared to placebo, with significant improvement in forced expiratory volume in 1 second (FEV₁), and a 75% reduction in daily oral corticosteroid use.

Benznidazole

In August 2017, the FDA announced the approval of benznidazole, the first medication for the treatment of Chagas disease, a parasitic infection caused by *Trypanosoma cruzi*.³ Chronic *T. cruzi* infection may result in cardiac and

gastrointestinal disease. Although more common in South America, Chagas disease affects approximately 200,000 people in the United States. The safety and efficacy of the drug was established in two phase 3 placebo-controlled trials in children 6-12 years of age. The percentage of children that became antibody negative was 60% in the benznidazole group compared to 14% in the controls. In the second study, the results were 55% and 5% for the two groups, respectively. The most common adverse effects were headache, abdominal pain, nausea, vomiting, rash, and hives. Serous dermatologic and nervous system reactions, as well as bone marrow suppression have also been reported.

Cerliponase alfa

Cerliponase alfa (Brineura™) is a recombinant form of human tripeptidyl peptidase (TPP1) developed for the management of TPP1 deficiency, also known as neuronal ceroid lipofuscinosis type 2 (CLN2), in children 3 years of age and older. A dose of 300 mg is infused into the CSF via an implanted reservoir and catheter every other week. The approval was supported by the results of an open-label dose-escalation study over 96 weeks.⁴ Twenty-four children from 3 to 8 years of age were enrolled. Of the 22 evaluated at week 96, 21 (95%) had no decline in the motor domain of the CLN2 clinical rating scale.

Deflazacort

Approval for deflazacort (Emflaza®), an oxazoline derivative of prednisolone, in the treatment of Duchenne muscular dystrophy (DMD) was based on a 52-week phase 3 randomized, double-blind, placebo-controlled multicenter study.⁵ Patients were randomized to receive deflazacort at a dose of either 0.9 mg/kg/day or 1.2 mg/kg/day, prednisone 0.75 mg/kg/day, or placebo for 12 weeks; after that point, patients in the placebo group were randomized to one of the active treatment groups. All treatment groups demonstrated significant improvement in muscle strength compared to placebo. Patients in the prednisone group had significantly more weight

gain. Subsequent studies have confirmed deflazacort's more favorable adverse effect profile.⁶ It is approved for use in patients 5 years of age and older with DMD.

Epinephrine

In November 2017, the FDA approved a lower dose epinephrine auto-injector (AUVI-Q[®]) for the emergency management of anaphylaxis or other severe hypersensitivity reactions in infants and toddlers.⁷ The new dosage strength, 0.1 mg, is designed for use in patients 7.5 to 15 kg, extending the range of patients covered by the current 0.15 mg and 0.3 mg devices. As with the other strengths, the 0.1 mg device should be held firmly against the thigh, through clothing if necessary. At the same meeting, the FDA approved a change in the labeling of all the AUVI-Q[®] devices shortening the time it must be held in place from 5 to 2 seconds after activation. Each auto-injector provides a single dose, with both oral and visual cues for use. The kit comes with two auto-injectors and a trainer.

L-Glutamine Oral Powder

L-glutamine (Endari[™]), was approved in 2017 for the treatment of sickle cell disease in adults and children 5 years of age and older.^{8,9} The approval was supported by a phase 3 randomized trial of 230 patients 5-58 years old with sickle cell disease who had two or more pain crises within the previous year. Patients were randomized to L-glutamine or placebo for the 48-week trial. The treatment group experienced fewer hospital visits for sickle cell pain crises requiring opioids or ketorolac compared to the controls (median 3 versus 4), fewer hospitalizations for sickle cell pain (median 2 versus 3), and fewer days in the hospital (median 6.5 days versus 11 days). Patients who received L-glutamine also had fewer episodes of acute chest syndrome (8.6% versus 23.1%).

Ozenoxacin 1% Cream

This new topical quinolone is approved for the treatment of impetigo in adults and children 2 months of age and older. Ozenoxacin (Xepi[™]) was approved based on the results of two phase 3 multicenter randomized, double-blind placebo-controlled studies. One of the studies has been published, showing a clinical success rate of 34.8% in the treatment group compared to 19.2% in the controls ($p = 0.003$), with a microbiological success rates of 79.2% and 56.6% at 6-7 days in the two groups, respectively.¹⁰

Tisagenlecleucel

Tisagenlecleucel (Kymriah[™]) is used for CD19-directed genetically modified autologous T cell immunotherapy.¹¹ The patient's T cells are modified by a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing cells. Tisagenlecleucel is approved for children and adults less than 25 years of age with refractory B-cell precursor acute

lymphoblastic leukemia. Approval was based on the results of a global phase 2 single-cohort study of 75 patients which demonstrated an overall survival rate of 90% (95% CI 81, 95) at 6 months and 76% (63, 86) at 12 months. Continued assessment of the study patients has shown the presence of tisagenlecleucel in the blood up to 20 months after a dose. Cytokine release syndrome occurred in 77% of patients, with 40% having transient neurologic events.

Voretigene neparvovec-rzyl

Approval for voretigene neparvovec-rzyl (Luxturna[™]), gene replacement therapy for retinal pigment epithelial-65 mutation-associated retinal dystrophy, was based on data from a single phase 3 clinical trial.¹² After 1 year of treatment, comparison of the patients in the treatment group and controls using change in mean bilateral multi-luminance mobility testing (MLMT) scores showed a difference of 1.6 (95% CI 0.72, 2.41, $p = 0.001$). Change in full-field light sensitivity threshold and mobility test scores also showed significant improvement with treatment.

New Pediatric Indications

A total of 54 new pediatric labeling changes were made by the FDA in 2017, with another six already announced in 2018.¹³ These included several new pediatric indications, as well as warnings and other safety data.

Abatacept

Approval for the use of abatacept (Orencia[®]) in the treatment of severely active polyarticular juvenile idiopathic arthritis (pJIA) was extended to patients 2 years of age and older. Supporting data came from a phase 3 global 24-month open-label study.¹⁴ Patients achieved target steady-state serum trough concentrations and showed improvement in pJIA symptoms.

Aliskiren

The FDA extended the approval for aliskiren (Tekturna[®]) for the treatment of hypertension to children 6 years of age and older. The approval was based on two randomized double-blind trials in children 6-17 years of age.

Antiretrovirals

Several agents previously approved for the management of HIV-1 infection in adults have received approval for use in pediatric patients. The combinations of emtricitabine and tenofovir (Descovy[®]) and elvitegravir, cobicistat, emtricitabine, and tenofovir (Genvoya[®]) were approved for use in children weighing at least 25 kg, while raltegravir (Isentress[®] HD) and the combination of elvitegravir, cobicistat, emtricitabine, and tenofovir (Stribild[®]) was approved for patients weighing at least 35 kg, while the combination of abacavir, dolutegravir, and lamivudine (Triumeq[®]) was approved for use in patients weighing at least 40 kg. Raltegravir (Isentress[®]) was also approved for use in HIV-

exposed neonates from 0-4 weeks of age and weighing at least 2 kg.

Cysteamine

The approval of cysteamine bitartrate (Procysbi®) to treat nephropathic cystinosis was expanded to include children as young as 1 year of age. It was previously approved for 2 years and older.

Daptomycin

The FDA extended the approval of daptomycin (Cubicin®) for the treatment of *Staphylococcus aureus* bacteremia and complicated skin and skin structure infections (cSSSI) to include children 1-17 years of age. Supporting data came from several studies, including a randomized trial in 389 children with cSSSI, where the clinical success rate for daptomycin (91%) was similar to that seen with clindamycin or vancomycin.¹⁵

Eslicarbazepine

Approval for the use of eslicarbazepine (Aptiom®) for partial-onset seizures was extended to include children 4 to 17 years of age. The extension was based on extrapolation from studies in adults and older children.

Everolimus

Oral everolimus tablets for the preparation of a suspension (Afinitor Disperz) were approved earlier this month for use in adults and children 2 years of age and older with tuberous sclerosis complex-associated partial-onset seizures. The phase 3 placebo-controlled EXIST-3 trial demonstrated a significant reduction in seizure frequency with everolimus as adjunctive therapy.

Fosphenytoin

The approval for fosphenytoin (Cerebyx®) was extended to include patients from birth to 17 years of age. Fosphenytoin is indicated for the treatment of generalized tonic-clonic status epilepticus, for the prevention and treatment of seizures occurring during neurosurgery, and as a short-term replacement for oral phenytoin.

Inhaled Products for Asthma

Several products received an extension for younger children in 2017. Tiotropium bromide (Spiriva® inhalation spray) and budesonide/formoterol fumarate (Symbicort® inhalation aerosol) were approved for children 6 years of age and older. Fluticasone propionate (ArmonAir™ RespiClick) and fluticasone propionate/salmeterol (AirDuo™ RespiClick) were approved for children 12 years and older.

Lacosamide

Use of oral lacosamide (Vimpat®) for the treatment of partial-onset seizures was extended to children 4 years of age and older. Approval was based on safety and efficacy data from over 300 children ranging from 4 to 17 years of age. Safety of the injection has not yet been established in children.

Luliconazole

The approval for luliconazole 1% cream (Luzu™) use in the treatment of tinea pedis and tinea cruris has been extended to include use in patients 2 years of age and older. Supporting data came from pharmacokinetic and safety studies showing comparable results to studies in adults, as well as a placebo-controlled trial.

Lurasidone

In March, the FDA approved a supplemental new drug application to extend the indications for lurasidone (Latuda®) for the treatment of major depressive episodes associated with bipolar disorder in children and adolescents between 10 and 17 years of age. Lurasidone is an atypical antipsychotic agent with high-affinity binding at serotonin 5-HT₇ receptors that is comparable to its affinity for dopamine-2 and 5-HT_{2A} receptors. In addition, it has moderate affinity for 5-HT_{1A} receptors, and minimal to no affinity for H₁ and M₁ receptors. Approval was based on a randomized, double-blind placebo-controlled phase 3 study in 347 children and adolescents.¹⁶ Lurasidone produced a significant improvement in Children's Depression Rating Scale, Revised (CDRS-R) scores, with a CDRS-R score of -21.0 after treatment, compared to -1.05 in the controls (effect size 0.45, p < 0.0001) and a significant improvement on Clinical Global Impression-Bipolar Version, Severity of Illness scores (-1.49 versus 0.45, effect size 0.44, p < 0.0001).

Ophthalmic drops

Several ophthalmic products received pediatric indications in the past year, including: brimonidine (Lumify™) for eye irritation, cetirizine (Zerviate™) for allergic conjunctivitis, and the combination of phenylephrine and ketorolac (Omidria®) for prevention of intraoperative miosis and reduction of postoperative pain. The age range for ciprofloxacin (Ciloxan®), gatifloxacin (Zymar®), and moxifloxacin (Vigamox®) for treatment of bacterial conjunctivitis was extended to patients 1 month of age and older.

Peramivir

Use of peramivir (Rapivab®) in the treatment of influenza was extended to include children 2 years of age and older. The drug is given as a single IV dose to patients who have been symptomatic for no more than 2 days.

Perampanel

The approval for perampanel (Fycompa™) as monotherapy for the treatment of partial-onset seizures with or without secondarily generalized seizures was extended to include patients 12 years of age and older. Perampanel had previously been approved as adjunctive therapy in this age range.

Ustekinumab

The use of ustekinumab (Stelara®) in patients with psoriasis has been extended to adolescents 12

years of age and older. Data from a multicenter, randomized, double-blind, placebo-controlled trial in 110 adolescents showed similar benefit and adverse effects as reported in adult studies.

Drugs in the FDA Pipeline

A wide variety of new drug applications (NDAs) were submitted to the Food and Drug Administration in 2017. Several of these agents are targeted at or have the potential for use in the pediatric population.

Cannabidiol

In the third quarter of 2017, GW Pharmaceuticals submitted an NDA for its proprietary cannabinoid product (Epidolex®) as an adjunctive therapy for the treatment of seizures in children and adults with Lennox Gastaut syndrome (LGS) or Dravet syndrome. Data supporting approval comes from three phase 3 trials in more than 1,000 patients. The submission has been granted both Rare Pediatric Disease and Orphan Drug designations, as well as a fast track designation.

Dasotraline

Sunovion Pharmaceuticals has submitted an NDA for dasotraline, its new treatment for attention deficit hyperactivity disorder (ADHD). Dasotraline is a unique dual-acting dopamine and norepinephrine reuptake inhibitor. The NDA includes the results of placebo-controlled safety and efficacy studies in more than 2,000 children and adults, including two year-long studies.

Golodirsen

A second exon-skipping therapy for patients with DMD will likely be undergoing assessment by the FDA this year. Golodirsen binds to exon 53 of dystrophin pre-mRNA, skipping this exon during mRNA processing and allowing for the production of truncated, but functional, dystrophin protein. The ESSENCE study, a global phase 3 randomized, double-blind, placebo-controlled trial, is currently enrolling patients.

Tafenoquine

At the end of 2017, GSK submitted an NDA for tafenoquine use in the prevention of relapse of *Plasmodium vivax* malaria in patients 16 years of age and older. Administered as a single dose, tafenoquine provides a clinical cure, preventing future relapse. Tafenoquine was developed through a partnership between GSK and the Medicines for Malaria Venture. Development of the drug began in 2008; it was given Breakthrough Therapy status by the FDA in 2013.

Summary

The FDA approved significantly more drugs in 2017 than in previous years. With the wealth of NDAs currently under evaluation, it is likely that 2018 will see the release of another large group of important additions to the market. While most new drug approvals will likely be for use in adults only, the success of FDA incentives to stimulate

pediatric research continues to add to the number of drugs with pediatric indications.

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