

PEDIATRIC PHARMACOTHERAPY



Volume 23 Number 7

July 2017

New Drug Approvals and New Pediatric Indications: An Update for Pediatric Healthcare Providers

Marcia L. Buck, PharmD, FCCP, FPPAG, BCPPS

Several new drugs have been approved by the Food and Drug Administration (FDA) in the past 6 months that benefit pediatric patients. While most are new formulations of drugs previously in use, there are a few new drug entities. The FDA has also approved the inclusion of pediatric patients in the indications for use for more than a dozen drugs since the beginning of the year. These expanded indications typically follow the submission of pediatric studies by the manufacturer in order to qualify for a 6-month extension of their patent rights under the Pediatric Exclusivity Program. This program, a part of the FDA Modernization Act of 1997, has resulted in new labeling information for a total of 692 drugs as of May 31, 2017. A database of new pediatric labeling is available on the FDA website at <https://www.accessdata.fda.gov/scripts/sda/sdNavigation.cfm?sd=labelingdatabase>.

Newly Approved Drug Products

Infliximab-abda

The first biosimilar of infliximab was approved by the FDA on April 24, 2017. Infliximab-abda (Renflexis®) is an alternative to Remicade®.^{1,2} Infliximab-abda is approved for the same indications, including use in patients 6 years of age and older with Crohn's disease, as well as ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis in adults. The recommended dose of infliximab is 5 mg/kg at 0, 2, and 6 weeks, followed by a dose every 8 weeks for pediatric Crohn's disease. Biosimilars, unlike generic products, are not identical to the originator, or reference, product. While not the same exact chemical entity, biosimilars have been found in premarketing testing to have no clinically meaningful differences from the reference

product. Unlike generic drugs that have the same name as the original (brand) product, biosimilars have the name of the original drug followed by a suffix to designate the difference.

Methotrexate Oral Suspension

Until the approval of a commercial methotrexate oral solution (Xatmep™) in April, it was necessary for patients and families needing a liquid preparation to find a hospital or compounding pharmacy able to prepare it for outpatient use. This often limited patient access to the drug in rural or underserved areas and increased both cost and time to have the prescription filled. The alternative, splitting or cutting tablets, creates a risk for family members or healthcare personnel for exposure to the drug through the skin during handling or inhalation of aerosolized particles. Silvergate Pharmaceuticals created a 2.5 mg/mL methotrexate solution that requires no further manipulation.^{3,4} It is recommended that it be refrigerated, but the solution is stable for 60 days at room temperature. Methotrexate oral solution is approved by the FDA for children with acute lymphoblastic leukemia or children with active polyarticular juvenile idiopathic arthritis who have had an insufficient response to non-steroidal anti-inflammatory agents.

Cerliponase alfa

The FDA has also approved cerliponase alfa (Brineura™) for use in pediatric patients 3 years of age and older with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), also referred to as tripeptidyl peptidase-1 deficiency.⁵⁻⁷ CLN2 is one of a group of disorders known as Batten disease. This rare inherited disease is typically diagnosed with the onset of symptoms at 2 to 4 years of age. The disease produces language delays, epilepsy,

and ataxia, with progression to myoclonus and vision loss. Cerliponase alfa is a recombinant form of human tripeptidyl peptidase-1. It is administered into the CSF through a surgically-implanted intraventricular access device and reservoir. The recommended dose is 300 mg given every other week by an intraventricular infusion over 4 to 5 hours. The efficacy of cerliponase alfa was determined in an open-label dose escalation study in 22 symptomatic children.⁸ Their motor and language skills were compared to a historical control group of 42 untreated children. Patients receiving treatment had significantly less decline in walking compared to the controls.

The most common adverse effects reported with the drug include bradycardia, hypotension, hypersensitivity, changes in CSF protein levels, vomiting, seizures, hematoma, headache, irritability, pleocytosis, jitteriness, and infection related to the intraventricular infusion device.⁹ The FDA has required the manufacturer, BioMarin Pharmaceuticals, to conduct a 10-year safety study of the drug, as well as a study to evaluate the efficacy and safety in younger patients so that treatment may be initiated at a younger age.

Epinephrine Injection

In June, the FDA approved a new epinephrine 0.3 mg pre-filled syringe for IM or subcutaneous injection for the emergency treatment of anaphylaxis or other severe hypersensitivity reactions.^{10,11} The new product, Symjepi™ (Adamis Pharmaceuticals) is an alternative to EpiPen®. It is supplied in a package of two syringes. An image of the syringe is available on the manufacturer's website at <http://www.adamispharmaceuticals.com/products/>. A lower dose pediatric version is currently being evaluated by the FDA. The manufacturer anticipates having the product available for purchase by fall. No price has been set yet, but the manufacturer has indicated that the price will be lower than the average retail price of \$368 for a package of two EpiPens®.

Once-Daily ADHD Treatments

Two new products for the management of attention deficit/hyperactivity disorder (ADHD) were also approved by the FDA in June. A new once-daily capsule of amphetamine salts was approved for patients 13 years of age and older with ADHD.^{12,13} Shire's mixed salts of a single-entity amphetamine product (Mydayis™) contains three different types of coated beads that release drug at separate intervals, producing up to 16 hours of symptom control. This is the longest duration of action from a single dose of any

central nervous system stimulant currently on the market in the United States.

Mydayis™ has undergone extensive testing in adolescents and adults, with 16 premarketing clinical trials enrolling more than 1,600 patients. The efficacy and safety of the drug was studied in a multicenter, randomized double-blind placebo-controlled study of 84 adolescents (13-17 years of age). This crossover study compared treatment with 12.5 or 25 mg capsules to placebo in a classroom-like setting. Active drug treatment resulted in statistically significant differences in testing performance at 2, 4, 8, 12, 14, and 16 hours post-dose, based on the ADHD Rating Scale IV and the Permanent Product Measure of Performance (PERMP). The adverse effect profile was similar to that seen with other once daily amphetamine products. There were no serious adverse effects, and none of the patients discontinued treatment as the result of an adverse effect.

A new extended-release orally disintegrating tablet (ODT) formulation of methylphenidate (Cotempla XR-ODT™) was approved for use in children and adolescents from 6 to 17 years of age with ADHD.^{14,15} Like most other once-daily products on the market, methylphenidate XR-ODT provides 12 hours of symptom control. It reflects continued expansion of ODT products from Neos Therapeutics. Their extended-release amphetamine ODT (Adzenys XR-ODT™) was approved for the US market in June 2016. The studies supporting the safety and efficacy of methylphenidate XR-ODT will be reviewed in a subsequent issue of *Pediatric Pharmacotherapy*.

New Pediatric Labeling

Fluticasone propionate

In January, the FDA extended the indications for two corticosteroids for asthma. The approval for fluticasone propionate (ArmonAir™ RespiClick®) and the combination of fluticasone propionate and salmeterol (AirDuo™ RespiClick®) were extended to include use in the maintenance treatment of asthma in patients 12 years of age and older.

Budesonide/formoterol fumarate dehydrate

The approval for the combination of budesonide and formoterol (Symbicort® inhalation aerosol) was extended to include patients 6 to 12 years of age with asthma. Safety and efficacy in this population was found to be similar to that observed in older adolescents and adults.

Elvitegravir, cobicistat, emtricitabine/tenofovir

The FDA-approved indication for this combination product (Stribild[®]) was extended to include pediatric patients with HIV who are 12 years of age and older. Patients must weigh at least 35 kg at the initiation of treatment to ensure appropriate dosing with the strengths of the four components in the currently available tablet. The approval for the drug was based on the results of a 48-week pharmacokinetic, safety, and efficacy study conducted in 50 treatment-naïve patients demonstrating its benefit.

Lurasidone hydrochloride

The use of lurasidone (Latuda[®]), an atypical or second generation antipsychotic used in the treatment of schizophrenia or for irritability associated with autistic disorder, was extended to adolescents 13 to 17 years of age. The approval was based on the results of a 6-week, placebo-controlled trial of 326 adolescents with schizophrenia. Earlier clinical studies also support its use in adolescents.¹⁶

Acetaminophen

The indication for acetaminophen injection (Ofirmev[®]) was extended to include treatment of pediatric patients from birth to 2 years of age. The decision to extend approval to infants was based on data demonstrating effective treatment of fever and an adverse effect profile similar to that seen in older children.

Lisdexamfetamine

The approval for lisdexamfetamine (Vyvanse[®]) was extended to children with ADHD 6 years of age and older. The release of a new strawberry-flavored chewable tablet formulation accompanied the announcement. The chewable tablets are available in 10 mg, 20 mg, 30 mg, 40 mg, 50 mg, and 60 mg strengths and may be substituted on a mg-per-mg basis with the capsule formulation.

Tiotropium bromide

In February, the FDA expanded the indication for tiotropium bromide (Spiriva[®] Respimat Inhalation Spray) to include long-term maintenance treatment of asthma in patients 6 to 11 years of age. The approval was supported by three clinical trials demonstrating the safety and efficacy of the drug in this age group. Studies in younger children are ongoing.

Fosphenytoin

The FDA approval for fosphenytoin sodium (Cerebyx[®]) was extended in March to include use in patients from birth to 17 years of age for the treatment of generalized tonic-clonic status

epilepticus, the prevention or treatment of seizures occurring during neurosurgery, and as a temporary replacement for oral phenytoin.

Barium Sulfate

The approval for barium sulfate (Liquid E-Z-Paque[®]) was extended to patients from birth to 17 years of age requiring radiographic examination of the esophagus, stomach, or small bowel.

Moxifloxacin Ophthalmic Solution

Use of moxifloxacin ophthalmic solution (Vigamox[®]) was extended to infants less than 1 year of age.

Ciprofloxacin and Gatifloxacin Ophthalmic Solutions

The FDA indications for ciprofloxacin and gatifloxacin ophthalmic drops (Ciloxan[®] and Zymar[®]) were extended to include treatment of bacterial conjunctivitis in infants 1 month of age and older. These products had previously been approved for pediatric patients over 1 year of age.

Daptomycin

Daptomycin (Cubicin[®]) was approved for use in children 1 to 17 years of age with complicated skin and skin structure infections (SSSI). Results of a pharmacokinetic, safety, and efficacy study conducted by the manufacturer in children with SSSI were similar to those of studies conducted in adults. Earlier retrospective studies support the efficacy of daptomycin in children, with an estimated clinical success rate of 81% to 93%.^{17,18}

Abatacept

Approval for the subcutaneous use of abatacept (Orencia[®]) was extended to include children 2 years of age and older with severe active polyarticular juvenile idiopathic arthritis, in combination with methotrexate. The safety and efficacy of the auto-injector device or intravenous administration have not yet been established in children.

Iodixanol

In April, the approval of iodixanol 320 mg/mL (Visipaque[™]) was extended to include use for coronary computed tomography angiography in children 12 years of age and older.

Ledipasvir and Sofosbuvir

Approval for the combination of ledipasvir and sofosbuvir (Harvoni[®]) was extended to include pediatric patients 12 years of age and older weighing at least 35 kg. This product is indicated for the treatment of chronic hepatitis C virus genotypes 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis.

Sofosbuvir

Sofosbuvir (Sovaldi®) was approved for use in combination with ritonavir for the treatment of children with chronic hepatitis C virus genotypes 2 or 3 infection who are 12 years of age and older and weigh at least 35 kg. It is approved for patients without cirrhosis or with compensated cirrhosis. The weight restriction for both Harvoni® and Sovaldi® reflects the lowest point at which the currently available adult dosage formulations will provide an appropriate dose.

Cetirizine Ophthalmic Solution

The approval for cetirizine eye drops (Zerviate™) was extended on May 5, 2017 to include children 2 years of age and older for the treatment of ocular itching related to an allergic reaction.

Summary

A wide variety of new drugs and new pediatric indications have recently been approved by the FDA that will be of benefit to children. These changes represent continued interest by pharmaceutical manufacturers in the pediatric population and the continued value of incentives for conducting pediatric studies and developing new dosage formulations for children. For additional information on FDA approvals and labeling changes, as well as safety alerts, all healthcare providers are encouraged to sign up for email updates at www.fda.gov or follow the FDA on Facebook or Twitter.

References

1. FDA approves Renflexis. Drugs.com. April 24, 2017. Available at: <https://www.drugs.com/newdrugs/fda-approves-renflexis-infliximab-abda-biosimilar-remicade-4519.html> (accessed 6/20/2017).
2. Renflexis prescribing information. Samsung Bioepis Co., Ltd. April 2017. Available at https://www.merck.com/product/usa/pi_circulars/r/renflexis/r_enflexis_pi.pdf (accessed 6/20/2017).
3. FDA approves Xatmep. Drugs.com. April 26, 2017. Available at <https://www.drugs.com/newdrugs/fda-approves-xatmep-methotrexate-oral-solution-4520.html> (accessed 6/20/2017).
4. Xatmep prescribing information. Silvergate Pharmaceuticals, Inc. April 2017. Available at <http://silvergatepharma.com/wp-content/uploads/2017/04/PI-4-26-17.pdf> (accessed 6/20/2017).
5. FDA Approves Brineura (cerliponase alfa) for the treatment of CLN2 disease, a form of Batten disease and ultra-rare pediatric brain disorder in children. Cision PR Newswire. April 27, 2017. Available at: <http://www.prnewswire.com/news-releases/fda-approves-brineura-cerliponase-alfa-for-the-treatment-of-cln2-disease-a-form-of-batten-disease-and-ultra-rare-pediatric-brain-disorder-in-children-300447385.html> (accessed 6/20/2017).
6. Brineura prescribing information. BioMarin Pharmaceuticals, Inc. April 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761052lbl.pdf (accessed 6/20/2017).
7. Markham A. Cerliponase alfa: first global approval. Drugs 2017; DOI: 10.1007/s40265-017-0771-8. [Epub ahead of print].

8. Gissen P, Schulz A, Specchio N, et al. Intracerebroventricular cerliponase alfa (BMN 190) in children with CLN2 disease: results from a phase 1/2, open-label, dose-escalation study [abstract]. Dev Med Child Neurol 2017;59(Suppl 1):7-8.
9. Schulz A, Specchio N, Gissen P, et al. Long-term safety and efficacy of intracerebroventricular enzyme replacement therapy with cerliponase alfa in children with CLN2 disease: interim results from an ongoing multicenter, multinational extension study [abstract no. 302]. Mol Genet Metab 2017;120(1-2):S120.
10. FDA approves Symjepi. Drugs.com. June 15, 2017. Available at <https://www.drugs.com/newdrugs/adamis-pharmaceuticals-receives-fda-approval-symjepi-epinephrine-pre-filled-syringe-4543.html> (accessed 7/1/2017).
11. Symjepi prescribing information. Adamis Pharmaceuticals Corporation. June 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207534lbl.pdf (accessed 6/29/2017).
12. Shire, plc. U.S. FDA approves Mydayis (mixed salts of a single-entity amphetamine product) – a new once-daily option for ADHD symptom control in patients 13 years and older. Cision PR Newswire. June 20, 2017. Available at <http://www.prnewswire.com/news-releases/shire-plc-us-fda-approves-mydayistm-mixed-salts-of-a-single-entity-amphetamine-product---a-new-once-daily-option-for-adhd-symptom-control-in-patients-13-years-and-older-629760653.html> (accessed 7/1/2017).
13. Mydayis prescribing information. Shire US Inc. June 2017. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022063s000lbl.pdf (accessed 6/21/2017).
14. Brooks M. FDA clears new methylphenidate formulation for ADHD. Medscape. June 20, 2017. Available at <http://www.medscape.com/viewarticle/881844> (accessed 6/29/2017).
15. Cotempla XR-ODT prescribing information. Neos Therapeutics Inc. June 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205489s000lbl.pdf (accessed 7/1/2017).
16. Findling RL, Goldman R, Chiu YY, et al. Pharmacokinetics and tolerability of lurasidone in children and adolescents with psychiatric disorders. Clin Ther 2015;37(12):2788-97.
17. Syriopoulou V, Dailiana Z, Dmitriv N, et al. Clinical experience with daptomycin for the treatment of gram-positive infections in children and adolescents. Pediatr Infect Dis J 2016;35(5):511-6.
18. Garazzino S, Castagnola E, Di Gangi M, et al. Daptomycin for children in clinical practice experience. Pediatr Infect Dis J 2016;35(6):639-41.

Contributing Editor: Marcia Buck, PharmD
Editorial Board: Kristi N. Hofer, PharmD
Clara Jane Snipes, RPh
Susan C. Mankad, PharmD

Pediatric Pharmacotherapy is available on the University of Virginia School of Medicine website at <https://med.virginia.edu/pediatrics/opportunities/pharmacotherapy-newsletter/>. For comments, contact us at mlb3u@virginia.edu.