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Pediatric Updates from the Food and Drug Administration

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The Food and Drug Administration (FDA) approved 25 novel drugs and biologics in 2018 and another 21 in the first quarter of 2019. While monoclonal antibodies and biosimilars continue to dominate the new approvals, a wide range of drugs have been introduced in the United States during this time. Several of these products carry a pediatric indication, but the majority are currently only approved for use in adults. Many of these drugs have the potential to be of benefit in the pediatric patient population and may eventually receive pediatric labeling. This issue of the newsletter will review these new treatment options, as well as granted new pediatric indications and drugs currently under FDA review.

New Drug and Drug Product Approvals

Burosumab

The first monoclonal antibody to treat children and adults with x-linked hypophosphatemia (XLH), burosumab (Crysvita®) was approved in 2018. XLH, a rare inherited form of rickets, affects approximately 15,000 patients in the United States and causes bowed legs and short stature, as well as bone, joint, and dental pain. The approval of burosumab was based on the results of four clinical trials conducted in 148 adults and 65 children. In an open-label study of burosumab in 52 children 5-12 years of age, mean serum phosphorus levels increased from 2.4 + 0.40 mg/dL at baseline to 3.4 + 0.45 mg/dL at week 64.

Cannabidiol

In 2018, the first proprietary cannabinoid product (Epidiolex®) was approved as an adjunctive therapy for the treatment of seizures in adults and children 2 years of age and older with Lennox Gastaut syndrome (LGS) or Dravet syndrome occurred in 2018. Cannabidiol was the first drug to be approved specifically for the treatment of patients with Dravet syndrome. Data supporting approval came from three phase 3 trials enrolling more than 1,000 pediatric and adult patients.

Clobazam Oral Film

Clobazam has been an important component in the management of LGS and other refractory seizure disorders since its approval in 2011. A new oral film (Sympazan™) was recently approved to provide an alternative for patients unable to swallow the tablets or large volumes of the oral suspension. The berry-flavored film is available in 5 mg, 10 mg, and 20 mg strengths.

Digital Inhaler

Teva Pharmaceutical Industries introduced their new albuterol digital inhaler (ProAir® Digihaler™) at the end of 2018. This is the first digital inhaler; it includes built-in sensors that connect to a mobile app to provide data on inhaler use to the patient, family, and potentially to healthcare providers. In addition to measuring when the inhaler is used, it evaluates inspiratory flow. The ProAir® Digihaler™ is approved by the FDA for use in patients 4 years of age and older.

Elapegademase-lvlr

The enzyme replacement therapy, elapegademase-lvlr (Revcovi™), has been approved for children and adults with adenosine deaminase severe combined immune deficiency (ADA-SCID). It is a PEGylated recombinant form of adenosine deaminase that supplements the patient's endogenous levels without the need to rely on animal sources.

Emapalumab-lzsg

The FDA approved the first drug specifically indicated for the treatment of primary hemophagocytic lymphohistiocytosis (HLH) in 2018. It is indicated for use in patients with progressive, refractory, or recurrent disease. The efficacy of emapalumab-lzsg (Gamifant®) was demonstrated in a study of 27 children with HLH who failed to respond to or were unable to tolerate traditional HLH therapy. Sixty-three percent of the patients responded to treatment, and 70% were able to proceed to stem cell transplant.

Epoetin alfa-epbx
The first biosimilar for epoetin (Retacrit™) was approved last year. As a biosimilar, epoetin alfa-epbx has no clinically significant differences in potency, purity, or safety compared to the original biological product. Biosimilars, however, are not considered interchangeable products. The availability of biosimilars is intended to provide competition, potentially reducing patient costs and increasing accessibility. Epoetin alfa-epbx carries the same indications as the original product and is approved for the treatment of anemia in children with cancer receiving chemotherapy or those with chronic kidney disease.

Hexavalent Vaccine
In December, the FDA approved the first product to contain six vaccines in the childhood immunization series (Vaxelis®). It contains diphtheria and tetanus toxoids and acellular pertussis adsorbed, inactivated poliovirus, Haemophilus b conjugate (meningococcal protein conjugate), and hepatitis B (recombinant) vaccines. The hexavalent vaccine was developed through a joint venture between Sanofi and Merck. It is currently in production and is expected to be available in 2020 when a sustainable supply can be maintained.

Lanadelumab
The first monoclonal antibody for the treatment of types I and II hereditary angioedema (HAE), lanadelumab-flyo (Takhzyro™) was approved by the FDA for patients 12 years of age and older. Lanadelumab, a plasma kallikrein inhibitor, was approved based on the results of a multicenter randomized, double-blind placebo-controlled trial in 125 adolescents and adults.[1] The percentage of patients without an HAE attack for the entire 26-week treatment period was 44%, 31%, and 39% in the patients given 300 mg lanadelumab every 2 weeks, 300 mg every 4 weeks, and 150 mg given every 4 weeks respectively, compared to 2% of placebo patients. An open-label continuation study demonstrated a sustained benefit.

Methylphenidate delayed-release, extended-release
The new delayed-release, extended-release methylphenidate product, Jornay PM™, was approved by the FDA for the treatment of ADHD in children 6 years of age and older last year. This unique product uses the Delexis® drug delivery platform to provide a dosage formulation that could be given at night to delay absorption, resulting in effective serum methylphenidate concentrations at breakfast and continuing throughout the day.

Moxidectin
River blindness, caused by the parasitic worm *Onchocerca volvulus*, is a devastating tropical illness endemic in lower income countries. Moxidectin was developed though a collaboration of Medicines Development for Global Health and the World Health Organization Special Program for Research and Training in Tropical Diseases for the treatment of river blindness. In a phase 3 study, moxidectin produced significantly greater suppression of microfilariae in skin than ivermectin. It is currently approved for patients 8 years of age and older.

Sarecycline
Several acne products were approved in the past year, including sarecycline (Seysara™), a first-in-class tetracycline-derivative. It provides a new option for oral treatment of non-nodular moderate-to-severe acne vulgaris in patients 9 years of age and older. Sarecycline is taken once daily and typically produces improvement within 3 weeks after starting treatment. Improvement in Investigator Global Assessment scores of acne severity in the two premarketing studies were 21% and 22.6% in the treatment groups, compared to 10.5% and 15.3% in the placebo groups, respectively.

Stiripentol
A second drug for the treatment of refractory seizures in patients with Dravet syndrome, stiripentol (Diacomit®) was approved in December 2018. Stiripentol is a direct allosteric modulator of $GABA_A$ receptors and offers a unique mechanism of action that benefits both patients with and without sodium channel α-1 subunit gene (SCN1A) mutations. In phase 3 trials, over 60% of patients experienced a 50% or greater reduction in seizure frequency.

Tafenoquine
Tafenoquine has been approved by the FDA for the prevention of relapse of *Plasmodium vivax* malaria in patients 16 years of age and older. Administered as a single dose, it is designed to provide a clinical cure, preventing future relapse. Tafenoquine was developed through a partnership between GSK and the Medicines for Malaria Venture. Development began in 2008; it was given Breakthrough Therapy status in 2013.

Tezacaftor/ivacaftor and ivacaftor
The FDA approved the combination tezacaftor/ivacaftor and ivacaftor (Symdeko®) in February 2018 for the treatment cystic fibrosis in patients 12 years of age and older with two copies of the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or patients with one mutation that is responsive to tezacaftor/ivacaftor. This is the third product from Vertex Pharmaceuticals for patients with CF. Efficacy and safety for this combination was established in the EVOLVE and EXPAND trials.[3,4] These two randomized, double-blind, placebo-controlled, phase 3, crossover trials enrolled more than 750 patients. In the EXTEND continuation study, the benefit in lung function seen in the EVOLVE and EXTEND studies was sustained for up to 48 weeks.

Tretinoin Lotion
A new lotion formulation of tretinoin (Altreno™ lotion) was approved for the treatment of moderate-to-severe acne vulgaris to children ages 9 years and older. Approval of this product was based on the results of two multicenter, randomized, double-blind, 12-week trials conducted in 1,640 adolescents and adults, as well as an open-label pharmacokinetic study.[5] Mean absolute reduction in inflammatory lesions was significantly greater in the treatment groups; 13.1 and 13.9 in the patients using tretinoin lotion, compared to 10.6 and 10.7 in the vehicle-only control groups.

New and Extended Pediatric Indications
In addition to manufacturer incentives provided through the FDA's Pediatric Research Equity Act (PREA), the National Institutes of Child Health and Human Development (NICHD) provides funding for research in off-patent drugs through the Best Pharmaceuticals for Children Act (BCPA). A total of 773 pediatric labeling changes have been made since the inception of these programs.[6] Labeling changes include not only new indications and age-based extensions, but also new pharmacokinetic, dosing, and safety information. The following examples highlight the range of new information and extended indications approved during the past 15 months.

Dasatinib
Use of dasatinib (Sprycel®) was extended to pediatric patients one year and older with newly diagnosed Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia in combination with chemotherapy. Efficacy in newly diagnosed B-cell precursor Ph+ ALL was evaluated in a single cohort of 78 children, median age 10 years, taking part in a larger multicenter, multiple-cohort study. The 3-year event-free survival rate was 64.1% (95% CI: 52.4, 74.7). At the end of induction, 75 patients (96%) had a bone marrow biopsy with <5% lymphoblasts; 76 patients (97%) achieved this goal by the end of consolidation.

Dupilumab
The approval for dupilumab (Dupixent®) for the treatment of uncontrolled moderate-to-severe atopic dermatitis was recently extended to patients 12 to 17 years of age. The drug targets the interleukin (IL-4/IL-13) pathway and is the first monoclonal antibody for atopic dermatitis to be approved in the pediatric population. Dupilumab can be used with corticosteroids or alone. In a phase 3 trial, dupilumab produced significantly greater improvement in the Eczema Area and Severity Index compared to placebo (66% versus 24%).

Fosapepitant
The indication for fosaprepitant injection (Emend®) has been extended to include infants and children 6 months of age and older for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy. This approval was based on extrapolation of data from studies of fosaprepitant injection in adults, as well as additional safety, efficacy and pharmacokinetic data in pediatric patients. Efficacy was also supported by data from a controlled study of an oral 3-day aprepitant regimen in pediatric patients 6 months to 17 years.

Perampanel
The indication for perampanel (Fycompa®) has been extended to include treatment of partial onset seizures, with or without secondarily generalized seizures, in patients 4 years and older. Use of perampanel in this population is based on evidence from several controlled trials, including an open-label study with a 41-week extension phase, pharmacokinetic data from adult and pediatric patients, and safety data in 225 pediatric patients 4 years to less than 12 years of age.[7]

Voriconazole
Approval for voriconazole (Vfend®) was extended to patients 2 years of age and older with invasive aspergillosis, disseminated candidiasis, and candidemia. The approval was based on the results of two multicenter open-label non-comparative trials in children 2 to 18 years of age. Thirty-one children were enrolled in the first study. Global response, defined as clinical improvement and a 50% or greater reduction in radiologic lesions, was reported in 40% of the patients 2-11 years of age and 75% of the group 12 years and older. The second study enrolled 22 children 2-18 years of age. Global response rates were 70% in the group with invasive candidiasis and 86% in those with esophageal candidiasis.

Drugs in the FDA Pipeline
A wide variety of new drug applications (NDAs) were submitted to the FDA in 2018 and the first months of 2019. Several are expected to be approved for use in children at the time of marketing, while others have the potential for use in the pediatric population but will require subsequent study.

Fenfluramine
The review of a third new antiseizure medication for the treatment of patients with Dravet syndrome, fenfluramine (Fintepla®), was recently refused by the FDA. The decision to postpone review was based on a failure to include the necessary data to assess the effects of chronic administration of fenfluramine and the inclusion of an incorrect version of a clinical dataset which prevented completion of the review process. The manufacturer is currently working with the FDA to comply with the request for the additional

documents and anticipates review of their NDA later this year.[8]

Golodirsen

An NDA for a second exon-skipping therapy for patients with Duchenne muscular dystrophy (DMD), golodirsen (SRP-4053), was submitted to the FDA in February. Golodirsen binds to exon 53 of dystrophin pre-mRNA. Skipping this exon during mRNA processing allows production of truncated, but functional, dystrophin protein. The efficacy and safety of the drug were established in 25 boys with DMD known to have a deletion of the dystrophin gene amenable to exon 53 skipping. The drug produced both an increase in the quantity of dystrophin expression compared to baseline and increased dystrophin intensity as measured by immunohistochemistry. Golodirsen is currently being studied in the ESSENCE study, a global, randomized double-blind, placebo-controlled trial assessing the safety and efficacy of golodirsen with casimersen, an exon 45 skipping agent also be developed by the manufacturer.

Luspatercept

The erythroid maturation agent luspatercept is a first-in-class treatment for anemia associated with myelodysplastic syndromes and beta-thalassemia. While not yet studied in children, a recently published phase 2 trial in adults with beta-thalassemia included patients as young as 20 years of age. The phase 3 BELIEVE trial also included young adults.[9] This randomized, double-blind, placebo-controlled study was conducted at 65 sites in 15 countries and enrolled 336 patients, with a median age of 30 years. Patients received luspatercept 1 mg/kg or placebo by subcutaneous injection every 21 days for up to 48 weeks in addition to standard supportive care. The results of these trials, as well as those of a phase 3 trial in MSD-related anemia were included in the NDA.

Minocycline Foam

A new topical minocycline foam is currently being evaluated by the FDA for the treatment of moderate-to-severe acne vulgaris in adults and children 9 years of age and older. The NDA includes data from two placebo-controlled phase 3 trials.[10] In both studies, the drug met the primary endpoints with statistically significant difference in improvement in inflammatory lesion count and in Investigator Global Assessment (IGA) treatment scores.

Oxycodone Extended-Release Tablets

The number of abuse-deterrent opioid products continued to grow over the past year as prescribers look for new ways to mitigate the risks for opioid misuse. Intellipharmaceutics International recently submitted an NDA for their new oxycodone extended-release tablet (Rexista®) formulated with their proprietary abuse-deterrent design, referred to as the novel point of divergence drug delivery system (nPODDDS™). This system alters the product to discourage chewing or licking of the tablet and makes crushing of the tablet difficult, reducing the likelihood of insufflation, inhalation, or injection. Apart from this change, the product will be equivalent to traditional oxycodone tablets.

Summary

While most new drug approvals carry indications for use only in adults, a number of these agents have application in the pediatric patient population. Continued work by the FDA and the NICHD to provide support and incentives for pediatric research have resulted in significant strides in gaining pediatric approval of both new drugs and older drugs that have been used off-label.

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