APhA DrugInfoLine®

August 2018

Focus on Immunizations

Advising on this article: John D. Grabenstein

August 6, 2018

DTaP vaccines are safe, but take care to prevent vaccination-related errors

Key Point

An in-depth review of data from the Vaccine Adverse Event Reporting System (VAERS) on DTaP-based vaccines over a 19-year period showed no new or unexpected safety signals, with the most common adverse events being injection-site reactions and fever. Nonserious vaccination errors were also identified as an issue.

Source URL:

http://www.aphadruginfoline.com/focus-immunizations/dtap-vaccines-are-safe-take-care-prevent-vaccination-related-errors

Endocrinology

Advising on this article: Frank Pucino

August 6, 2018

Denosumab is a good option for patients receiving glucocorticoids

Key Point

Use of denosumab (Prolia—Amgen) for 12 months was shown to be both noninferior and superior to risedronate on select bone mineral density endpoints for patients newly initiating glucocorticoids or those continuing therapy, according to results of a trial published in The Lancet Diabetes and Endocrinology.

Source URL:

http://www.aphadruginfoline.com/endocrinology/denosumab-good-option-patients-receiving-glucocorticoids

Alternative Medicines Corner

Advising on this article: Nicole M. Maisch

August 14, 2018

Nearly one-third of children use dietary supplements

Key Point

An analysis of data from the National Health and Nutrition Examination Surveys (NHANES) from 2003 to 2014 published in JAMA Pediatrics found that approximately 33% of children and young adults (aged 0–19 y) use dietary supplements that range from multivitamins to melatonin to omega-3 fatty acids.

Source URL:

http://www.aphadruginfoline.com/alternative-medicines-corner/nearly-one-third-children-use-dietary-supplements

Endocrinology

Advising on this article: Frank Pucino

August 14, 2018

Updated guideline released on use of testosterone therapy for hypogonadism

Key Point

The Endocrine Society released an updated clinical practice guideline on use of testosterone therapy for men with hypogonadism in the Journal of Clinical Endocrinology and Metabolism. The guideline recommends that men with symptoms of low testosterone be tested and treatment be given to hypogonadal men (<65 y) to induce or maintain secondary sex characteristics and improve symptoms of testosterone deficiency, but only after the risks and benefits of therapy are thoroughly discussed.

Source URL:

http://www.aphadruginfoline.com/endocrinology/updated-guideline-released-use-testosterone-therapy-hypogonadism

Focus on Anticoagulation Care

Advising on this article: Sarah Ray

August 21, 2018

Real-world outcomes of direct oral anticoagulants versus warfarin

Key Point

Apixaban (Eliquis—Bristol-Myers Squibb, Pfizer) appeared to be the safest direct oral anticoagulant compared with warfarin with respect to major, intracranial, and gastrointestinal bleeding, whereas rivaroxaban (Xarelto—Janssen) and low-dose apixaban were associated with an increased risk of all-cause mortality compared with warfarin, according to results of a prospective open cohort study published in BMJ.

Source URL:

http://www.aphadruginfoline.com/focus-anticoagulation-care/real-world-outcomes-direct-oral-anticoagulants-versus-warfarin

Rheumatology

Advising on this article: Arthur A. Schuna

August 21, 2018

I.M. glucocorticoids may be an option for painful hip osteoarthritis

Key Point

A small exploratory study showed that an I.M. injection of triamcinolone acetate into the gluteus muscle for patients with painful hip osteoarthritis improved pain at rest and during activity over a 12-week period compared with placebo.

Source URL:

http://www.aphadruginfoline.com/rheumatology/im-glucocorticoids-may-be-option-painful-hip-osteoarthritis

Focus on Immunizations

Advising on this article: John D. Grabenstein

August 28, 2018

Reduced influenza vaccine effectiveness observed in a select birth cohort

Key Point

An analysis published in the Journal of Infectious Diseases of vaccine effectiveness (VE) over five influenza seasons (2010–16) showed reduced effectiveness during the 2015–16 influenza season compared with previous seasons. This reduced effect was most prominent in adults born between 1958 and 1979 (i.e., people in their 40s and 50s) compared with all other birth cohorts combined.

Source URL:

http://www.aphadruginfoline.com/focus-immunizations/reduced-influenza-vaccine-effectiveness-observed-select-birth-cohort

Oncology

Advising on this article: Gary C. Yee

August 28, 2018

Practice-changing data for nonmetastatic, castrate-resistant prostate cancer

Key Point

Two trials published in the New England Journal of Medicine showed that use of the next-generation androgen-receptor blockers apalutamide (Erleada—Janssen) or enzalutamide (Xtandi—Astellas) in men with nonmetastatic, castration-resistant prostate cancer (nmCRPC) significantly prolonged metastasis-free survival (MFS) and improved several other secondary endpoints, compared with placebo.

Source URL:

http://www.aphadruginfoline.com/oncology/practice-changing-data-nonmetastatic-castrate-resistant-prostate-cancer

New Drug Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 1, 2018	
Lusutrombopag ***(Mulpleta—Shionogi)*** **New drug targets thrombocytopenia in adults with chronic liver disease**	FDA approved lusutrombopag, a once-daily, orally administered, small molecule thrombopoietin receptor agonist, for treatment of thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a medical or dental procedure. Approval was based on two randomized, double-blind, placebo-controlled trials involving 312 patients with chronic liver disease and severe thrombocytopenia who were undergoing an invasive procedure and had a platelet count of less than 50 x 109/L. Patients were randomized 1:1 to receive 3 mg of lusutrombopag or placebo once daily for up to 7 days. In one trial, 78% of patients (38/49) receiving lusutrombopag required no platelet transfusion prior to the primary invasive procedure, compared with 13% (6/48) who received placebo. In the second trial, 65% (70/108) of patients who received lusutrombopag required no platelet transfusion prior to the primary invasive procedure or rescue therapy for bleeding from randomization through 7 days after the procedure, compared with 29% (31/107) receiving placebo. The most common adverse reaction (?3% of patients) was headache. The recommended lusutrombopag dosage is 3 mg orally once daily with or without food for 7 days.

Source URL:

http://www.aphadruginfoline.com/new-drug-approvals/new-drug-targets-thrombocytopenia-adults-chronic-liver-disease

Alerts and Recalls

Generic Name (Trade Name—Company)	**Uses**/Notes
August 3, 2018 **Azithromycin** ***(Zithromax, Zmax—Pfizer, others)*** **Increased risk of cancer relapse with long-term use of azithromycin after donor stem cell transplant**	FDA is warning that the antibiotic azithromycin should not be given long term to prevent an inflammatory lung condition known as bronchiolitis obliterans syndrome in patients with cancers of the blood or lymph nodes who undergo a donor stem cell transplant. Results of a clinical trial found an increased rate of relapse in cancers affecting the blood and lymph nodes, including death, in these patients. Bronchiolitis obliterans syndrome is caused by inflammation and scarring in the airways of the lungs, resulting in severe shortness of breath and dry cough. Patients with cancer who undergo stem cell transplants from donors are at risk for bronchiolitis obliterans syndrome.There are no known effective antibiotic treatments that prevent the syndrome, and azithromycin is not approved for this use. It is an FDA-approved antibiotic used to treat many types of infections affecting the lungs, sinuses, skin, and other parts of the body. The drug, which has been used for more than 26 years, is sold under the brand names Zithromax and Zmax and as generics by many different drug companies. Pfizer, the manufacturer of brand name azithromycin, is providing a Dear Healthcare Provider letter on this safety issue to health professionals who care for patients undergoing donor stem cell transplants. FDA is reviewing additional data and will communicate its conclusions and recommendations when the review is complete. Patients who have had a stem cell transplant should not stop taking azithromycin without first consulting with their health care provider.

Source URL:

http://www.aphadruginfoline.com/alerts-and-recalls/increased-risk-cancer-relapse-long-term-use-azithromycin-after-donor-stem-cell

New Drug Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 16, 2018	
Mogamulizumab-kpkc ***(Poteligeo—Kyowa Kirin)*** **FDA approves treatment for two rare types of non-Hodgkin lymphoma**	FDA approved mogamulizumab-kpkc injection for I.V. use for the treatment of adult patients with relapsed or refractory mycosis fungoides (MF) or Sézary syndrome (SS) after at least one prior systemic therapy. This approval provides a new treatment option for patients with MF and is the first FDA approval of a drug specifically for SS. The agent is a monoclonal antibody that binds to a CC chemokine receptor type 4 (CCR4) found on some cancer cells. Approval was based on a clinical trial of 372 patients with relapsed MF or SS who received either mogamulizumab-kpkc or a type of chemotherapy called vorinostat. Progression-free survival was longer for patients taking mogamulizumab-kpkc (median 7.6 mo) compared with patients taking vorinostat (median 3.1 mo). In clinical trials, the most common adverse effects of treatment included rash, infusion-related reactions, fatigue, diarrhea, musculoskeletal pain, and upper respiratory tract infection. Serious warnings include the risk of dermatologic toxicity, infusion reactions, infections, autoimmune problems, and complications of stem cell transplantation that uses donor stem cells (allogeneic) after treatment with the drug.

Source URL:

http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-treatment-two-rare-types-non-hodgkin-lymphoma

New Drug Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 16, 2018	
Patisiran	FDA approved patisiran infusion for the treatment of peripheral nerve disease (polyneuropathy) caused by hereditary transthyretin-mediated amyloidosis (hATTR) in adult patients. This is the first FDA-approved treatment for patients with polyneuropathy caused by hATTR, a rare, debilitating, and often fatal genetic disease characterized by the buildup of abnormal amyloid protein in peripheral nerves, the heart, and other organs. It is also the first FDA approval of a new class of drugs called small interfering ribonucleic acids (siRNAs). siRNAs work by silencing a portion of RNA involved in causing the disease. More specifically, patisiran encases the siRNA into a lipid nanoparticle to deliver the drug directly into the liver, in an infusion treatment, to alter or halt the production of disease-causing proteins. The agent is designed to interfere with RNA production of an abnormal form of the protein transthyretin (TTR). By preventing the production of TTR, the drug can help reduce the accumulation of amyloid deposits in peripheral nerves, improving symptoms and helping patients better manage the condition. Efficacy was shown in a clinical trial involving 225 patients, 148 of whom were randomly assigned to receive a patisiran infusion once every three weeks for 18 months, and 77 of whom were randomly assigned to receive a placebo infusion at the same frequency. The patients who received patisiran had better outcomes on measures of polyneuropathy, including muscle strength, sensation (pain, temperature, numbness), reflexes, and autonomic symptoms (blood pressure, heart rate, digestion) compared with those receiving the placebo infusions. Patisiran-treated patients also scored better on assessments of walking, nutritional status, and the ability to perform activities of daily living. The most common adverse reactions reported by patients in clinical trials included flushing, back pain, nausea, abdominal pain, dyspnea, and headache. All patients who participated in the clinical trials received

(Onpattro—Alnylam Pharmaceuticals)

First-of-its kind targeted RNA-based therapy approved for rare peripheral nerve disease

premedication with a corticosteroid, acetaminophen, and antihistamines (H1 and H2 blockers) to reduce the occurrence of infusion-related reactions.

Patients may also experience vision problems, including dry eyes, blurred vision, and eye floaters (vitreous floaters). Use of the agent can cause a decrease in serum vitamin A levels, so patients should take a daily Vitamin A supplement at the recommended daily allowance.

Source URL:

http://www.aphadruginfoline.com/new-drug-approvals/first-its-kind-targeted-rna-based-therapy-approved-rare-peripheral-nerve-disease

New Drug Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 16, 2018	
Migalastat ***(Galafold—Amicus Therapeutics U.S.)*** **New oral medication targets a rare genetic disorder, Fabry disease**	FDA approved migalastat, the first oral medication for the treatment of adults with Fabry disease, a rare and serious genetic disorder caused by mutations in the alpha-galactosidase A (GLA) gene located on the X-chromosome. The disease results from buildup of globotriaosylceramide (GL-3) in blood vessels, the kidneys, the heart, the nerves, and other organs. It is estimated that classic Fabry disease (the most severe type) affects approximately one in 40,000 males. The later-onset type is more frequent and in some populations may occur in one in 1,500 to 4,000 males. Patients with Fabry disease develop slowly progressive kidney disease, cardiac hypertrophy, arrhythmias, stroke, and early death. Efficacy was demonstrated in a 6-month, placebo-controlled clinical trial in 45 adults with Fabry disease. Patients treated with migalastat had a greater reduction in GL-3 in blood vessels of the kidneys (as measured in kidney biopsy samples) compared with patients on placebo. Migalastat's safety was studied in four clinical trials that included 139 patients with Fabry disease. The most common adverse drug reactions were headache, nasal and throat irritation, urinary tract infection, nausea, and fever.

Source URL:

http://www.aphadruginfoline.com/new-drug-approvals/new-oral-medication-targets-rare-genetic-disorder-fabry-disease

New Drug Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 16, 2018	
Segesterone acetate and ethinyl estradiol vaginal system	FDA has approved segesterone acetate and ethinyl estradiol vaginal system under the trade name Annovera. The combined hormonal contraceptive is the first vaginal ring contraceptive that can be used for an entire year. Annovera is a reusable donut-shaped (ring), nonbiodegradable, flexible vaginal system that is placed in the vagina for 3 weeks, followed by 1 week out of the vagina, at which time women may experience a period (a withdrawal bleed). This schedule is repeated every 4 weeks for 1 year (thirteen 28-day menstrual cycles). The ring is washed and stored in a compact case for the 7 days not in use. It does not require refrigeration prior to dispensing and can withstand storage temperatures up to 30° C (86° F). Efficacy and safety of Annovera were studied in three open-label clinical trials that included healthy women ranging in age from 18 to 40 years. The results showed that about 2 to 4 women out of 100 may get pregnant during the first year they use Annovera. Annovera carries a boxed warning on cigarette smoking and serious cardiovascular events. Women older than 35 who smoke should not use Annovera. Cigarette smoking increases the risk of serious cardiovascular events from combination hormonal contraceptive use. Annovera also is contraindicated and should not be used in women with a high risk of arterial or venous thrombotic diseases; current or history of breast cancer or other estrogen- or progestin-sensitive cancer; liver tumors, acute hepatitis, or severe (decompensated) cirrhosis; undiagnosed abnormal uterine bleeding; hypersensitivity to any of the Annovera components; and use of Hepatitis C drug combinations containing ombitasvir/paritaprevir/ritonavir, with or without dasabuvir. The most common adverse effects are similar to those of other combined hormonal contraceptive products, such as headache/migraine, nausea/vomiting, yeast

(Annovera—The Population Council)

New vaginal ring provides 1 year of birth control

infections, abdominal pain, dysmenorrhea, breast tenderness, irregular bleeding, diarrhea, and genital itching.

FDA is requiring postmarketing studies to further evaluate the risks of venous thromboembolism and the effects of CYP3A-modulating drugs and tampon use on the pharmacokinetics of Annovera.

Source URL:

http://www.aphadruginfoline.com/new-drug-approvals/new-vaginal-ring-provides-1-year-birth-control

Supplemental Approvals

Generic Name (Trade Name—Company)

Uses/Notes

August 17, 2018

Epinephrine auto-injector

FDA has approved the first generic version of EpiPen and EpiPen Jr (epinephrine) auto-injector for the emergency treatment of allergic reactions, including those that are life-threatening, in adults and pediatric patients who weigh more than 33 pounds. Teva Pharmaceuticals gained approval to market its generic epinephrine auto-injector in 0.3-mg and 0.15-mg strengths.

The EpiPen is intended to automatically inject a dose of epinephrine into a person's thigh to stop an allergic reaction. FDA has approved several epinephrine auto-injector products under new drug applications to treat anaphylaxis, including EpiPen, Adrenaclick, and Auvi-Q. In addition, "authorized generic" versions of EpiPen and Adrenaclick are marketed without the brand names.

An authorized generic is made under the brand name's existing new drug application using the same formulation, process, and manufacturing facilities used by the brand name manufacturer. The labeling or packaging is, however, changed to remove the brand name or other trade dress. In some cases, a company may choose to sell an authorized generic at a lower cost than the brand-name drug product.

This epinephrine injection (auto-injector) is intended for immediate administration to patients. When given intramuscularly or subcutaneously, it has a rapid onset and short duration of action. Epinephrine works by reducing swelling in the airway and increasing blood flow in the veins.

The most common adverse effects associated with epinephrine injection are anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, and/or respiratory difficulties. Rare cases of serious skin and soft tissue infections have been reported following use of the drug. In patients with heart disease, use of epinephrine injection may cause chest pain or abnormal heart beats. Following use of epinephrine injection, patients should seek immediate medical or hospital care.

(Epinephrine pen—Teva)

FDA approves first generic version of EpiPen

Epinephrine should not be injected into the vein, buttock, fingers, hands, or feet. To minimize risk of injection-site injury, movement of the leg should be limited during injection.

Source URL:

http://www.aphadruginfoline.com/supplemental-approvals/fda-approves-first-generic-version-epipen

New Drug Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 20, 2018	
Methylphenidate ***(Jornay PM—Ironshore Pharmaceuticals)*** **FDA approves ADHD agent with nighttime dosing**	FDA has approved a novel, extended-release formulation of methylphenidate for the treatment of ADHD in patients aged 6 years and older. It is taken once daily in the evening at 8:00, instead of immediately upon waking, to provide early-morning symptom control. Timing of administration may be adjusted between 6:30 p.m. and 9:30 p.m. to optimize the tolerability and the efficacy the next morning and throughout the day. Effectiveness of methylphenidate was established in two separate Pivotal Phase III, multicenter, randomized, double-blind, placebo-controlled studies conducted in a total of 278 pediatric patients aged 6 to 12 years with a diagnosis of ADHD per *DSM-5* criteria. In addition to the traditional scales that assess efficacy in ADHD clinical trials, such as the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale and the ADHD Rating Scale (ADHD-RS-IV), Ironshore's pivotal trials assessed methylphenidate's efficacy in the early morning period using the morning subscale of the Parent Rating of Evening and Morning Behavior-Revised (PREMB-R AM) scale and the Before School Functioning Questionnaire (BSFQ). Ironshore plans to make the drug available commercially in the first half of 2019.

Source URL:

http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-adhd-agent-nighttime-dosing

Alerts and Recalls

Generic Name (Trade Name—Company)	**Uses**/Notes
August 20, 2018	
Thyroid tablets ***(Levothyroxine, liothyronine—Westminster Pharmaceuticals)*** **Thyroid medication recalled because of adulteration risk**	Westminster Pharmaceuticals is voluntarily recalling all lots of levothyroxine and liothyronine thyroid tablets in strengths of 15 mg, 30 mg, 60 mg, 90 mg, and 120 mg. These products are being recalled as a precaution because they were manufactured using active pharmaceutical ingredients that were sourced prior to FDA's Import Alert of Sichuan Friendly Pharmaceutical Co., which as a result of a 2017 inspection were found to have deficiencies with Current Good Manufacturing Practices (cGMP). Substandard cGMP practices could represent the possibility of risk being introduced into the manufacturing process. To date, Westminster Pharmaceuticals has not received any reports of adverse events related to this product. Because these products may be used in the treatment of serious medical conditions, patients taking the recalled medicines should continue taking their medicine until they have a replacement product. The products subject to recall are packed in 100-count bottles.To best identify the products, see this table.

Source URL:

http://www.aphadruginfoline.com/alerts-and-recalls/thyroid-medication-recalled-because-adulteration-risk

Alerts and Recalls

Generic Name (Trade Name—Company)	**Uses**/Notes
August 20, 2018	
Pembrolizumab, atezolizumab ***(Keytruda, Tecentriq—Merck, Genentech)*** **Updated prescribing info requires use of companion diagnostic test**	FDA has updated the prescribing information for pembrolizumab and atezolizumab to require use of an FDA-approved companion diagnostic test to determine PD-L1 levels in tumor tissue from patients with locally advanced or metastatic urothelial cancer who are cisplatin-ineligible. Two different companion diagnostic tests were approved by FDA, one for use with pembrolizumab (Dako PD-L1 IHC 22C3 PharmDx Assay [Dako North America]) and one for use with atezolizumab (Ventana PD-L1 [SP142] Assay (Ventana Medical Systems)]. The second-line indications in urothelial carcinoma for both drugs remain unchanged. The tests used in the trials to determine PD-L1 expression are listed in Section 14 of each drug label.

Source URL:

http://www.aphadruginfoline.com/alerts-and-recalls/updated-prescribing-info-requires-use-companion-diagnostic-test

Alerts and Recalls

Generic Name (Trade Name—Company)	**Uses**/Notes
August 20, 2018	
Porcine thyroid API	FDA is alerting active pharmaceutical ingredient (API) repackagers and distributors, finished drug manufacturers, and compounders that Sichuan Friendly Pharmaceutical Co. Limited, China, is recalling certain lots of porcine thyroid API because of inconsistent quality of the API. FDA recommends that manufacturers and compounders not use Sichuan Friendly's porcine thyroid API received since August 2015. This thyroid API comes from porcine (pig) thyroid glands and is used to make a non-FDA approved drug product, composed of levothyroxine and liothyronine, to treat hypothyroidism. FDA laboratory testing confirmed the Sichuan Friendly API has inconsistent levels of the active ingredients – levothyroxine and liothyronine – and should not be used to manufacture or compound drugs for patient use. Risks associated with over- or under- treatment of hypothyroidism could result in permanent or life-threatening adverse health consequences. FDA placed Sichuan Friendly on import alert 66-40 on March 22, 2018, based on current good manufacturing practice (CGMP) deviations observed during an FDA inspection. However, FDA confirmed Sichuan Friendly's thyroid API remains in the U.S. supply chain. Sichuan Friendly API may be repackaged and/or relabeled before it is further distributed, and not all of the repackaged/relabeled API identifies Sichuan Friendly as the original API manufacturer. Therefore, manufacturers and compounders who make levothyroxine and liothyronine drug products should contact their API supplier to verify the actual manufacturer of the thyroid API they received before using it. Sichuan Friendly's products may be labeled as "Thyroid Powder" or "Thyroid Powder USP." In addition, manufacturers and compounders who have received API made by Sichuan Friendly should quarantine the API and associated drug products. If manufacturers and compounders have API or drug

(No trade name—Sichuan Friendly Pharmaceutical Co.)

FDA alerts drug makers of a recall of porcine thyroid API from Sichuan Friendly Pharmaceutical Co. in China

products made from Sichuan Friendly API, FDA requests these companies contact FDA's regional offices.

FDA recommends patients talk to their health professional before they stop taking their combination levothyroxine and liothyronine thyroid medicine. FDA also recommends that patients discuss FDA-approved hypothyroidism treatment options with their doctors, as combination levothyroxine and liothyronine products are not FDA approved.

Source URL:

http://www.aphadruginfoline.com/alerts-and-recalls/fda-alerts-drug-makers-recall-porcine-thyroid-api-sichuan-friendly-pharmaceutical

New Drug Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 20, 2018	
Cyclosporine ophthalmic solution 0.09%	Sun Pharma announced FDA approval of cyclosporine ophthalmic solution 0.09% to increase tear production in patients with keratoconjunctivitis sicca (dry eye).
(Cequa—Sun Pharma)	
New solution treats dry eye disease	Approval was based on a Phase III trail showing that after 12 weeks of treatment, cyclosporine ophthalmic solution 0.09% showed statistically significant improvement in the primary endpoint, Schirmer's score (a measurement of tear production), compared with vehicle. Improvements in secondary endpoints (i.e. ocular staining assessments) were seen as early as 1 month after initiating treatment. The solution is dosed twice daily and will be available as a single-use vial.

Source URL:

http://www.aphadruginfoline.com/new-drug-approvals/new-solution-treats-dry-eye-disease

Supplemental Approvals

Generic Name (Trade Name—Company)

Uses/Notes

August 20, 2018

Ivacaftor

(Kalydeco—Vertex Pharmaceuticals)

First agent to target underlying cause of CF in children as young as 12 months

Vertex Pharmaceuticals announced FDA approval of ivacaftor to include use in children with cystic fibrosis (CF) aged 12 months to younger than 24 months who have at least one mutation in their cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to ivacaftor, based on clinical and/or in vitro assay data.

FDA approval for this indication was based on data from the ongoing Phase III open-label safety study (ARRIVAL) of 25 children with CF aged 12 months to younger than 24 months who have 1 of 10 mutations in the CFTR gene.

The study demonstrated a safety profile consistent with that observed in previous Phase III studies of older children and adults; most adverse events were mild or moderate in severity, and no patient discontinued because of adverse events. Two patients had elevated liver enzymes greater than eight times the upper limit of normal but continued to receive ivacaftor after a dose interruption.

The most common adverse events (?30%) were cough (74%), pyrexia (37%), elevated aspartate aminotransferase (37%), elevated alanine aminotransferase (32%), and runny nose (32%). Four serious adverse events were observed in two patients.

Mean baseline sweat chloride for the children in this study was 104.1 mmol/L (n = 14). Following 24 weeks of treatment with ivacaftor, the mean sweat chloride level was 33.8 mmol/L (n = 14). In the 10 participants with paired sweat chloride samples at baseline and week 24, there was a mean absolute change of -73.5 mmol/L.

Ivacaftor was previously approved for treatment of CF in patients aged 2 years and older who have 1 of 38 ivacaftor-responsive mutations in the CFTR gene, based on clinical and/or in vitro assay data.

Source URL:

http://www.aphadruginfoline.com/supplemental-approvals/first-agent-target-underlying-cause-cf-children-young-12-mon

ths

Supplemental Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 20, 2018	
Pembrolizumab ***(Keytruda—Merck)*** **Pembrolizumab approved in combination with chemotherapy for first-line treatment of metastatic nonsquamous NSCLC**	FDA approved pembrolizumab in combination with pemetrexed and platinum as first-line treatment of patients with metastatic, nonsquamous non–small cell lung cancer (NSqNSCLC), with no EGFR or ALK genomic tumor aberrations. Approval was based on the results of KEYNOTE-189, a randomized, multicenter, double-blind, active controlled study enrolling 616 patients receiving first-line treatment for metastatic NSqNSCLC. The trial demonstrated a statistically significant improvement in overall survival for patients randomized to pembrolizumab and chemotherapy in a prespecified interim analysis. The most common adverse reactions were fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, and pyrexia. The recommended pembrolizumab dose and schedule for this indication is 200 mg as an I.V. infusion over 30 minutes every 3 weeks.

Source URL:

http://www.aphadruginfoline.com/supplemental-approvals/pembrolizumab-approved-combination-chemotherapy-first-line-treatment

Supplemental Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 20, 2018	
Nivolumab	FDA granted accelerated approval to nivolumab for patients with metastatic small cell lung cancer (SCLC) with progression after platinum-based chemotherapy and at least one other line of therapy.
(Opdivo—Bristol-Myers Squibb)	Approval was based on demonstration of a durable overall response rate (ORR) in a subgroup of patients from CheckMate-032, a multicenter, open-label trial in patients with metastatic solid tumors. This subgroup comprised 109 patients with metastatic SCLC, with disease progression after platinum-based therapy and at least one other prior line of therapy, regardless of tumor PD-L1 status.
FDA grants nivolumab accelerated approval for third-line treatment of metastatic small cell lung cancer	All patients received nivolumab 3 mg/kg by I.V. infusion over 60 minutes every 2 weeks. The ORR was 12%. Responses were durable for 6 months or longer in 77%, 12 months or longer in 62%, and 18 months or longer in 39% of the 13 responding patients. PD-L1 tumor status did not appear to be predictive of response. Safety data were evaluated in 245 patients with metastatic SCLC with disease progression following platinum-based chemotherapy and received at least one dose of nivolumab at a dose of 3 mg/kg every 2 weeks. The most common (?20%) adverse reactions were fatigue, decreased appetite, musculoskeletal pain, dyspnea, nausea, diarrhea, constipation, and cough. Nivolumab was discontinued for adverse reactions in 10% of patients, and 25% of patients had at least one dose withheld for an adverse reaction. Serious adverse reactions occurred in 45% of patients. The most frequent (?2%) serious adverse reactions were pneumonia, dyspnea, pneumonitis, pleural effusion, and dehydration. The recommended dose and schedule of nivolumab for this indication is 240 mg every 2 weeks over 30 min.

Source URL:

http://www.aphadruginfoline.com/supplemental-approvals/fda-grants-nivolumab-accelerated-approval-third-line-treatment-metastatic

Supplemental Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 28, 2018	
Stiripentol ***(Diacomit—Biocodex)*** **Stiripentol now approved for seizures associated with Dravet syndrome**	FDA approved stiripentol for the treatment of seizures associated with Dravet syndrome, a rare form of epilepsy. Stiripentol is indicated for use in patients aged 2 years and older who are taking clobazam. There are no clinical data to support the use of stiripentol as monotherapy in Dravet syndrome. Dravet syndrome is a rare genetic condition that usually appears during the first year of life with prolonged fever-related seizures. Later, other types of seizures typically appear, including myoclonic seizures. In addition, status epilepticus, a potentially life-threatening state of continuous seizure activity requiring emergency medical care, may occur. Children with Dravet syndrome typically experience poor development of language and motor skills, hyperactivity, and difficulty relating to others. The most common adverse effects reported with stiripentol are somnolence, decreased appetite, agitation, impaired coordination and balance, weight loss, low muscle tone, nausea, tremor, dysarthria, and insomnia. Stiripentol must be dispensed with a patient Medication Guide that describes important information about the drug's uses and risks. As is true for many other drugs that treat epilepsy, the most serious risks include thoughts about suicide, attempts to commit suicide, feelings of agitation, new or worsening depression, aggression, and panic attacks.

Source URL:

http://www.aphadruginfoline.com/supplemental-approvals/stiripentol-now-approved-seizures-associated-dravet-syndrome

New Drug Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 28, 2018	
Lanadelumab ***(Takhzyro—Shire)*** **First-of-its-kind monoclonal antibody treats hereditary angioedema**	FDA approved lanadelumab, the first monoclonal antibody approved in the United States to treat patients aged 12 years and older with types I and II hereditary angioedema (HAE). HAE is a rare and serious genetic disease that affects an estimated 1 in 50,000 men and women with low levels of and poorly functioning C1-INH proteins. This results in recurrent, unpredictable episodes of severe swelling in different areas of the body, including the stomach, limbs, face, and throat. Type I is the most common and accounts for 85% of cases. Symptoms of HAE typically begin in childhood and worsen following puberty. Some patients may have many attacks each month, while others will go months without an attack. FDA based its approval on data from a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in 125 patients with HAE. Patients who received lanadelumab had clinically meaningful and statistically significant reductions in the rate of investigator-confirmed HAE attacks compared with placebo over a 6-month treatment period. The most common adverse reactions in clinical trials were injection-site reactions, upper respiratory infections, headache, rash, muscle pain, dizziness, and diarrhea.

Source URL:

http://www.aphadruginfoline.com/new-drug-approvals/first-its-kind-monoclonal-antibody-treats-hereditary-angioedema

New Drug Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 28, 2018	
Eravacycline ***(Xerava—Tetraphase Pharmaceuticals)*** **New agent approved for treatment of cIAI in patients aged 18 years and older**	Tetraphase Pharmaceuticals announced FDA approval of eravacycline for the treatment of complicated intra-abdominal infections (cIAI) in patients aged 18 years and older. In clinical trials, eravacycline was well tolerated and achieved high clinical cure rates in patients with cIAI, demonstrating statistical noninferiority to two widely used comparators—ertapenem and meropenem. To reduce the development of drug-resistant bacteria and maintain the effectiveness of eravacycline and other antibacterial drugs, eravacycline should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. Eravacycline is contraindicated for use in patients with known hypersensitivity to eravacycline or to tetracycline-class antibacterial drugs. Life-threatening hypersensitivity reactions have been reported with use of the drug. The most common adverse reactions observed in clinical trials (incidence ? 3%) were infusion-site reactions, nausea, and vomiting.

Source URL:

http://www.aphadruginfoline.com/new-drug-approvals/new-agent-approved-treatment-ciai-patients-aged-18-years-and-older

Supplemental Approvals

Generic Name (Trade Name—Company)

Uses/Notes

August 28, 2018

Loteprednol etabonate ophthalmic suspension

(Inveltys—Kala Pharmaceuticals)

First twice-daily ocular corticosteroid approved for postop pain and inflammation

Kala Pharmaceuticals announced FDA approval of loteprednol etabonate ophthalmic suspension 1% under the trade name Inveltys for the treatment of postoperative inflammation and pain following ocular surgery. It is the first twice-daily ocular corticosteroid approved for this indication.

In a news release, Kala stated that all other ocular steroids are approved for four-times-a-day dosing only, a dosing requirement that can lead to issues for both doctors and patients. Corticosteroids are the foundation of therapy for postocular surgery care, with the key goal of controlling inflammation and pain caused by surgical trauma to the eye.

In clinical trials, the most common adverse drug reactions were eye pain (1%) and posterior capsular opacification (1%). These reactions may have been the consequence of the surgical procedure.

Source URL:

http://www.aphadruginfoline.com/supplemental-approvals/first-twice-daily-ocular-corticosteroid-approved-postop-pain-and-inflammation

Supplemental Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 28, 2018	
Tretinoin 0.05% lotion ***(Altreno—Ortho Dermatologics)*** **First formulation of tretinoin in a lotion is approved for acne**	Ortho Dermatologics announced FDA approval of tretinoin 0.05% lotion as a topical treatment of acne vulgaris in patients aged 9 years and older. The product, the first formulation of a tretinoin in a lotion, has been shown to be effective and generally well tolerated. It spreads easily and is quickly absorbed into the skin, allowing patients with acne to easily incorporate the once-daily treatment into their skin care regimen, stated the news release. Extensive clinical data have shown that retinoids are highly effective in treating acne and are considered a cornerstone of topical therapy. However, a common perceived barrier to their use is that treatment with retinoids is associated with skin irritation, such as dryness, peeling, and sensitivity. Tretinoin lotion was evaluated in two identical multicenter, randomized, double-blind, vehicle-controlled Phase III studies totaling 1,640 patients to determine its safety and efficacy. The data demonstrated that use of the product resulted in statistically significant reductions in both inflammatory and noninflammatory lesions compared with placebo. The most common adverse reactions, occurring in greater than 1% of participants and greater than placebo, were dryness, pain erythema, irritation, and exfoliation. Sunscreen and protective clothing should be worn when sun exposure cannot be avoided. The product is expected to become available during the fourth quarter of 2018.

Source URL:

http://www.aphadruginfoline.com/supplemental-approvals/first-formulation-tretinoin-lotion-approved-acne

Alerts and Recalls

Generic Name (Trade Name—Company)	**Uses**/Notes
August 28, 2018	
CVS Health 12 Hour Sinus Relief Nasal Mist ***(No trade name—Product Quest Manufacturing)*** **CVS nasal spray recalled because of microbiological contamination**	Product Quest Manufacturing is voluntarily recalling lot #173089J of CVS Health 12 Hour Sinus Relief Nasal Mist, a clear, colorless liquid, to the consumer level. The product was found to have had microbiological contamination identified as *Pseudomonas aeruginosa.* More information is available here.

Source URL:

http://www.aphadruginfoline.com/alerts-and-recalls/cvs-nasal-spray-recalled-because-microbiological-contamination

Alerts and Recalls

Generic Name (Trade Name—Company)	**Uses**/Notes
August 28, 2018	
Hydrochlorothiazide tablets ***(No trade names—Accord Healthcare)*** **Product recalled nationwide because of labeling mix-up**	Accord Healthcare is voluntarily recalling one lot (#PW05264 – 46632 bottles, NDC 16729-182-01) of hydrochlorothiazide tablets 12.5 mg to the consumer level. A 100-count bottle was found to contain 100 spironolactone tablets 25 mg. Since the individual lot of the product is involved in a potential mix-up of labeling, Accord is recalling this individual lot from the market. Based on findings of both preliminary and interim investigations carried out at the manufacturing site, Accord believes that no other lots of hydrochlorothiazide tablets are involved in this mix-up. Accord became aware of this finding through a product complaint reported from a pharmacy. More information is available on FDA's website.

Source URL:

http://www.aphadruginfoline.com/alerts-and-recalls/product-recalled-nationwide-because-labeling-mix

Supplemental Approvals

Generic Name (Trade Name—Company)	**Uses**/Notes
August 30, 2018	
Lenvatinib ***(Lenvima—Eisai Inc.)*** **Lenvatinib has new indication for treatment of unresectable hepatocellular carcinoma**	FDA has approved lenvatinib capsules for first-line treatment of patients with unresectable hepatocellular carcinoma (HCC). Approval was based on an international, multicenter, randomized, open-label, noninferiority trial conducted in 954 patients with previously untreated, metastatic or unresectable HCC. Patients were randomized (1:1) to receive lenvatinib (12 mg orally once daily for patients with a baseline body weight of ?60 kg and 8 mg orally once daily for patients with a baseline body weight of <60 kg) or sorafenib (400 mg orally twice daily). Treatment continued until radiological disease progression or unacceptable toxicity. The trial demonstrated that lenvatinib was noninferior but not statistically superior to sorafenib for overall survival and a statistically significant improvement in progression-free survival compared with sorafenib. The overall response rate was higher for the lenvatinib arm compared with sorafenib (41% vs. 12% per mRECIST and 19% vs. 7% per RECIST 1.1). The most common adverse reactions observed in the lenvatinib-treated patients with HCC (?20%) in order of decreasing frequency were hypertension, fatigue, diarrhea, decreased appetite, arthralgia/myalgia, decreased weight, abdominal pain, palmar-plantar erythrodysesthesia syndrome, proteinuria, dysphonia, hemorrhagic events, hypothyroidism, and nausea. The recommended lenvatinib dosages for patients with HCC are the following: 12 mg orally once daily in patients 60 kg or greater actual body weight or 8 mg orally once daily in patients less than 60 kg actual body weight.

Source URL:

http://www.aphadruginfoline.com/supplemental-approvals/lenvatinib-has-new-indication-treatment-unresectable-hepatocellular-carcinoma