
A^{PhA} **DrugInfoLine[®]**

June 2018

[Neurology](#)

Advising on this article: Jack J. Chen

June 4, 2018

Teratogenic risk of antiepileptic drugs assessed

Key Point

A prospective analysis of data from a European pregnancy registry of antiepileptic drugs published in *Lancet Neurology* showed that use of valproate had the highest prevalence of major congenital abnormalities (10.3%), whereas agents such as oxcarbazepine (3.0%), lamotrigine (2.9%), and levetiracetam (2.8%) had the lowest prevalence. Also, dose dependency in prevalence was noted for select agents, with higher dosages having greater teratogenic risks than lower dosages.

Source URL:

<http://www.aphadruginfoline.com/neurology/teratogenic-risk-antiepileptic-drugs-assessed>

[OTC Medicines Corner](#)

Advising on this article: Tara Whetsel

June 4, 2018

Misinformation and barriers to emergency contraception persist

Key Point

Adolescent females inquiring about OTC emergency contraception (EC) were less likely to receive accurate information from pharmacy staff compared with adolescent males and physicians, and about 10% of adolescent patients regardless of gender were denied access to EC on the basis of their age, indicating that misinformation and access barriers to EC continue to exist, according to a report published in the Journal of Adolescent Health.

Source URL:

<http://www.aphadruginfoline.com/otc-medicines-corner/misinformation-and-barriers-emergency-contraception-persist>

[OTC Medicines Corner](#)

Advising on this article: Tara Whetsel

June 11, 2018

Can use of menthol-containing cough drops worsen a cough?

Key Point

Results of an observational study published in the Journal of the American Board of Family Medicine showed that use of cough drops was associated with a longer duration of cough compared with nonuse. A significant association was seen between cough severity and the average menthol dose per cough drop, the number of cough drops consumed per day, and the total amount of menthol consumed per day.

Source URL:

<http://www.aphadruginfoline.com/otc-medicines-corner/can-use-menthol-containing-cough-drops-worsen-cough>

[Oncology](#)

Advising on this article: Gary C. Yee

June 11, 2018

Costs of anticancer drugs have risen substantially, while clinical benefits remain similar

Key Point

An observational analysis assessing trends in costs of anticancer drugs over a 10-year period compared with clinical benefits in the Journal of Oncology Practice found that monthly prices of these medications increased by a mean of 9% annually, and incremental drug costs increased by 21% annually. The magnitude of clinical benefits of these agents did not experience a similar proportional positive change.

Source URL:

<http://www.aphadruginfoline.com/oncology/costs-anticancer-drugs-have-risen-substantially-while-clinical-benefits-remain-similar>

[Neurology](#)

Advising on this article: Jack J. Chen

June 19, 2018

Updated guideline released on use of disease-modifying therapies for patients with MS

Key Point

In April 2018, the American Academy of Neurology (AAN) published an updated guideline in Neurology on the use of disease-modifying agents for patients with multiple sclerosis (MS). The guideline focuses on who should start these therapies, which agents to initiate, switching between medications, and when to stop treatment.

Source URL:

<http://www.aphadruginfoline.com/neurology/updated-guideline-released-use-disease-modifying-therapies-patients-ms>

Focus on Diabetes Care

Advising on this article: Charles D. Ponte

June 19, 2018

Select antidiabetic medications associated with better mortality outcomes in patients with type 2 diabetes

Key Point

Use of sodium–glucose cotransporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) agonists were both associated with significantly lower all-cause mortality and cardiovascular (CV) mortality compared with dipeptidyl peptidase 4 (DPP-4) inhibitors and placebo/no treatment in patients with type 2 diabetes, according to results of a systematic review and network meta-analysis published in JAMA.

Source URL:

<http://www.aphadruginfoline.com/focus-diabetes-care/select-antidiabetic-medications-associated-better-mortality-outcomes-patients>

[Psychiatry](#)

Advising on this article: M. Lynn Crismon

June 26, 2018

Propranolol use in patients with posttraumatic stress disorder

Key Point

Administration of propranolol 90 minutes before reactivation of traumatic memories resulted in significant reductions in posttraumatic stress disorder (PTSD) symptoms compared with placebo, according to results of a small study published in the American Journal of Psychiatry.

Source URL:

<http://www.aphadruonline.com/psychiatry/propranolol-use-patients-posttraumatic-stress-disorder>

[OTC Medicines Corner](#)

Advising on this article: Tara Whetsel

June 26, 2018

Emollient bath additives not effective for childhood eczema

Key Point

Regular use of emollient bath additives for children aged 1 to 11 years who have atopic dermatitis/eczema, along with standard eczema management (e.g., leave-on emollients), did not result in any additional clinical benefits compared with standard management alone, according to results of an open-label trial published in BMJ.

Source URL:

<http://www.aphadruonline.com/otc-medicines-corner/emollient-bath-additives-not-effective-childhood-eczema>

Alerts and Recalls

Generic Name (Trade Name—Company)

June 1, 2018

Norethindrone acetate and ethinyl estradiol capsules and ferrous fumarate capsules

(Taytulla Softgel Capsules—Allergan)

Discovery of out-of-sequence capsules prompts recall of oral contraceptive

Uses/Notes

[Allergan issued](#) a voluntary recall of one lot (#5620706, Expiry May-2019) of norethindrone acetate and ethinyl estradiol capsules and ferrous fumarate capsules 1 mg/20 mcg, 6 x 28 physicians sample pack, indicated for use by women to prevent pregnancy. Allergan recently identified, through a physician report, that four placebo capsules were placed out of order in a sample pack. Specifically, the first four days of therapy had four nonhormonal placebo capsules instead of active capsules.

Oral contraceptive capsules that are taken out of sequence may place the user at risk for contraceptive failure and unintended pregnancy. The reversed order may not be apparent to either new users or previous users of the product, increasing the likelihood of taking the capsules out of order.

The product was distributed Nationwide to healthcare providers.

Please refer [here](#) to the affected lot number as well as photographs of the affected product.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/discovery-out-sequence-capsules-prompts-recall-oral-contraceptive>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

June 2, 2018

Estradiol vaginal inserts

(*Imvexxy—TherapeuticsMD*)

Estrogen product treats moderate to severe dyspareunia due to menopause

Uses/Notes

FDA approved [estradiol vaginal inserts](#) for treatment of moderate to severe vaginal pain associated with sexual activity, a symptom of vulvar and vaginal atrophy (VVA) due to menopause. It is the only product in its therapeutic class to offer a 4-mcg and 10-mcg dose, the 4 mcg representing the lowest approved dose of vaginal estradiol available.

VVA is a component of genitourinary syndrome of menopause, which may include but is not limited to genital symptoms of dryness, burning, and irritation; sexual symptoms such as decreased lubrication, discomfort, and pain; and urinary symptoms such as urgency, dysuria, and recurrent urinary tract infections. VVA is a chronic, progressive condition that leads to distressing symptoms and can worsen if not treated.

The product's mechanism of action is re-estrogenization of the tissue in and around the vagina. The formulation ensures that it dissolves completely without mess, so patients can use it any time of day by placing the softgel capsule in the lower part of the vagina to treat the vulva and vagina.

The inserts are administered daily for 2 weeks, followed by only twice-a-week dosing.

The most common adverse reaction (incidence ?3%) and greater than placebo was headache. No clinically significant differences in adverse events were observed between treatment and placebo groups.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/estrogen-product-treats-moderate-severe-dyspareunia-due-menopause>

[Alerts and Recalls](#)

Generic Name (Trade Name—Company)

June 2, 2018

Fluticasone propionate nasal spray

(No trade names—Apotex Corp.)

Nasal spray may contain small glass particles

Uses/Notes

FDA announced a [recall](#) of one lot of fluticasone propionate nasal spray 50 mcg per spray, 120 metered sprays (lot# NJ4501, expiration date July 2020). The product may contain small glass particles that could block the actuator, impact the functionality of the pump, and cause local trauma to the nasal mucosa in individuals who use it.

The issue was discovered through a customer complaint.

The spray is indicated for treatment of seasonal and perennial allergic rhinitis and management of sinus pain and pressure associated with allergic rhinitis in patients 4 to 17 years of age.

Patients, wholesalers, retailers, hospitals, or institutions should stop use and distribution of the remaining units and quarantine immediately.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/nasal-spray-may-contain-small-glass-particles>

Alerts and Recalls

Generic Name (Trade Name—Company)

June 2, 2018

Follitropin alfa injection

(Gonal-f RFF Redi-ject, Gonal-f Multi-Dose—EMD Serono)

FDA warns of stolen fertility drugs

Uses/Notes

FDA is alerting health professionals, patients, and the drug supply chain of [stolen injectable fertility medications](#) Gonal-f RFF Redi-ject, Gonal-f Multi-Dose (follitropin alfa injection). Patients who have product with these [lot numbers](#) should not use them.

All product with these lot numbers were in this stolen shipment. The lot numbers are located on the flap of each box, below the tamper-proof seal and next to the 2D barcode.

The products were stolen in Italy on May 17, 2018, and were intended to be shipped to the United States. EMD Serono of Rockland, MA, reported the theft of more than 16,000 packages of follitropin alfa injection to FDA on May 18, 2018.

Drug supply chain stakeholders that receive or possess these lot numbers must [notify](#) FDA via [Form FDA 3911](#). Anyone who has received suspicious or unsolicited offers to purchase follitropin alfa injection products since May 17, 2018, should contact [FDA Office of Criminal Investigations](#) at 800-551-3989.

Drug supply chain stakeholders should continue to remain vigilant when buying or selling these products and check the lot number to prevent stolen product from entering the drug supply chain.

Patients, health professionals, and drug supply chain stakeholders should check the product and label for signs of tampering before using.

FDA also reminds health professionals, patients, and drug supply chain stakeholders to purchase products only from licensed wholesale distributors and pharmacies. See FDA's [Know Your Source](#) and [BeSafeRx](#) programs for more information.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/fda-warns-stolen-fertility-drugs>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

June 4, 2018

Baricitinib

Uses/Notes

[Eli Lilly and Incyte announced](#) FDA approval of a 2-mg dose of baricitinib, a once-daily oral medication to treat moderately to severely active rheumatoid arthritis (RA) in adults who have had an inadequate response to one or more tumor necrosis factor (TNF)–inhibitor therapies.

Use of baricitinib in combination with other Janus kinase inhibitors or biologic disease–modifying antirheumatic drugs (bDMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine, is not recommended. Baricitinib may be used as monotherapy or in combination with methotrexate or other nonbiologic DMARDs.

Approval was based on a clinical trial program that included the RA-BEACON study, a randomized, double-blind, placebo-controlled study in which patients were randomly assigned to receive baricitinib 2 mg, baricitinib 4 mg or placebo, in addition to conventional DMARDs they were currently using. The study included 527 patients who had an inadequate response or intolerance to one or more TNF-inhibitor therapies. Patients could have had prior therapy with other bDMARDs.

The study results showed significantly higher ACR20 response rates and improvement in all individual ACR20 component scores at week 12 with use of baricitinib. Patients treated with baricitinib had significantly higher rates of ACR20 response versus patients treated with placebo at week 12 (49% of baricitinib-treated patients versus 27% of placebo-treated patients).

Baricitinib also demonstrated early symptom relief, with ACR20 responses seen as early as week 1. Patients reported significant improvements in physical function according to the Health Assessment Questionnaire Disability Index (HAQ-DI) (recording an average score of 1.71 before treatment and 1.31 at week 12) compared with placebo-treated patients (who recorded an average score of 1.78 before treatment and 1.59 at week 12).

Baricitinib is approved with a boxed warning for the risk

(*Olumiant—Eli Lilly, Incyte*)

FDA approves 2-mg dose of baricitinib to treat moderately to severely active RA in adults

of serious infections, malignancies, and thrombosis. Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving baricitinib

Lymphoma and other malignancies have been observed in patients treated with baricitinib as well. In addition, thrombosis—including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, some fatal—have occurred in some patients.

Other warnings and precautions include gastrointestinal perforations, laboratory abnormalities (including neutropenia, lymphopenia, anemia, liver enzyme elevations, and lipid elevations), and a warning against use of live vaccines with baricitinib.

The most common adverse events in clinical trials included upper respiratory tract infections, nausea, herpes simplex, and herpes zoster.

As part of the approval, the companies have agreed to conduct a randomized, controlled clinical trial to evaluate the long-term safety of baricitinib in patients with RA.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-2-mg-dose-baricitinib-treat-moderately-severely-active-ra-adults>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

June 5, 2018

Pegfilgrastim-jmdb

(*Fulphila—Mylan GmbH*)

First pegfilgrastim biosimilar helps reduce the risk of infection during cancer treatment

Uses/Notes

FDA approved [pegfilgrastim-jmdb](#) as the first biosimilar to pegfilgrastim (Neulasta) to decrease the chance of infection as suggested by febrile neutropenia in patients with nonmyeloid (non–bone marrow) cancer who are receiving myelosuppressive chemotherapy that has a clinically significant incidence of febrile neutropenia.

FDA's approval of the new biosimilar was based on a review of evidence that included extensive structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data that demonstrates pegfilgrastim-jmdb is biosimilar to pegfilgrastim. It has been approved as a [biosimilar](#), not as an [interchangeable product](#).

The most common adverse effects are bone pain and pain in extremities. Patients with a history of serious allergic reactions to human granulocyte colony–stimulating factors such as pegfilgrastim or filgrastim products should not take the new biosimilar.

Serious adverse effects from treatment include rupture of the spleen, acute respiratory distress syndrome, serious allergic reactions including anaphylaxis, acute inflammation of the kidney, an abnormally high level of white blood cells, capillary leak syndrome, and the potential for tumor growth. Fatal sickle cell crises also have occurred.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/first-pegfilgrastim-biosimilar-helps-reduce-risk-infection-during-cancer>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

June 8, 2018

Methoxy polyethylene glycol-epoetin beta (*Mircera—Vifor Pharma*)

Approval expanded for anemia associated with CKD in pediatric patients on dialysis

Uses/Notes

FDA approved [methoxy polyethylene glycol-epoetin beta](#) for the treatment of pediatric patients aged 5 to 17 years on hemodialysis who are converting from another erythropoietin-stimulating agent (ESA) after their hemoglobin level was stabilized with an ESA.

Approval was based on data from an open-label, multiple dose, multicenter, dose-finding trial in 64 pediatric patients (aged 5–17 y) with chronic kidney disease (CKD) on hemodialysis and had stable hemoglobin (Hb) levels while previously receiving another ESA (epoetin alfa/beta or darbepoetin alfa). Patients were administered methoxy polyethylene glycol-epoetin beta intravenously once every 4 weeks for 20 weeks. After the first administration, dosage adjustments were permitted to maintain target Hb levels.

Efficacy was based on maintaining Hb levels within target levels in the above clinical trial, and also from extrapolation from trials the agent in adult patients with CKD. The safety findings observed in pediatric patients were consistent with those previously reported in adults.

For conversion from another ESA, Mircera is dosed intravenously once every 4 weeks based on total weekly epoetin alfa or darbepoetin alfa dose at time of conversion. Full prescribing information is available at [Mircera PI](#).

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/approval-expanded-anemia-associated-ckd-pediatric-patients-dialysis>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

June 8, 2018

Rituximab

(Rituxan—Genentech)

FDA approves first biologic therapy for pemphigus vulgaris

Uses/Notes

[Genentech announced](#) FDA approval of rituximab to treat adults with moderate to severe pemphigus vulgaris (PV), a rare, serious, potentially life-threatening condition characterized by progressive painful blistering of the skin and mucous membranes.

Rituximab is the first biologic therapy approved by FDA for PV and the first major advancement in treatment of the disease in more than 60 years. The agent is now approved to treat four autoimmune diseases.

Approval was based on data from the Ritux 3 trial, a randomized, controlled trial conducted in France that used Roche-manufactured, European Union (EU)-approved rituximab product as the clinical trial material. The study compared the Ritux 3 regimen (EU-approved rituximab product plus short-term corticosteroids [CS]) to CS alone as a first-line treatment in patients with newly diagnosed moderate to severe pemphigus. The primary endpoint of the study was complete remission at month 24 without use of steroids for 2 or more months.

Results of the study showed that 90% of patients with PV treated with the Ritux 3 regimen met the endpoint, compared with 28% of patients with PV who were treated with CS alone. These results supported rituximab's efficacy in treating patients with moderate to severe PV, while tapering off CS therapy.

Rituxan can cause serious adverse effects that can lead to death, including severe skin and mouth reactions, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy.

Common adverse effects include infusion reactions, infections (with fever and chills), body aches, tiredness, and nausea.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/fda-approves-first-biologic-therapy-pemphigus-vulgaris>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

June 8, 2018

Venetoclax

Uses/Notes

[FDA granted regular approval](#) to venetoclax for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received at least one prior therapy.

Approval was based on MURANO, a randomized (1:1), multicenter, open-label trial of venetoclax with rituximab (VEN+R) versus bendamustine with rituximab (B+R) in 389 patients with CLL who had received at least one prior line of therapy. Patients in the VEN+R arm completed a 5-week ramp-up venetoclax schedule and then received venetoclax 400 mg once daily for 24 months measured from the rituximab start date.

Rituximab was initiated after venetoclax ramp-up and given for six cycles (375 mg/m² intravenously on cycle 1, day 1 and 500 mg/m² intravenously on day 1 of cycles 2–6, with a 28-day cycle length). The comparator arm received six cycles of B+R (bendamustine 70 mg/m² on days 1 and 2 of each 28-day cycle and rituximab at the above described dose and schedule).

Efficacy was based on progression-free survival (PFS) as assessed by an independent review committee. After a median follow-up of 23 months, the median PFS was not reached in the VEN+R arm and was 18.1 months (95% CI 15.8–22.3) in the B+R arm (hazard ratio [HR] 0.19 [95% CI 0.13–0.28]; *P* < 0.0001). The overall response rate was 92% in the VEN+R arm compared with 72% for those treated with B+R.

In patients treated with VEN+R, the most common adverse reactions (incidence ≥20%) were neutropenia, diarrhea, upper respiratory tract infection, fatigue, cough, and nausea. Grade 3 or 4 neutropenia developed in 64% of these patients, and grade 4 neutropenia developed in 31%.

Serious adverse reactions occurred in 46% of patients. Serious infections developed in 21% of patients, most commonly pneumonia (9%).

Due to rapid reduction in tumor volume, tumor lysis syndrome (TLS) is an important identified risk with

(Venclexta—AbbVie, Genentech)

FDA approves new drug for CLL or SLL, with or without 17 p deletion, after one prior therapy

venetoclax treatment. See the prescribing information for TLS risk stratification, prophylaxis, and monitoring.

All approved venetoclax regimens begin with a 5-week ramp-up. Full prescribing information is available at [Venclexta PI](#).

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-new-drug-cll-or-sll-or-without-17-p-deletion-after-on-e-prior-therapy>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

June 14, 2018

Pembrolizumab

Uses/Notes

FDA granted [accelerated approval](#) of pembrolizumab to treat patients with cancer whose unresectable or metastatic solid tumors have a specific genetic feature (biomarker), referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.

MSI-H and dMMR tumors contain abnormalities that affect the proper repair of DNA inside the cell. Tumors with these biomarkers are most commonly found in colorectal, endometrial, and gastrointestinal cancers but also less commonly appear in cancers arising in the breast, prostate, bladder, thyroid gland, and other places. Approximately 5% of patients with metastatic colorectal cancer have MSI-H or dMMR tumors.

Pembrolizumab works by targeting the PD-1/PD-L1 cellular pathway. By blocking this pathway, the drug may help the body's immune system fight the cancer cells. FDA previously approved the agent to treat certain patients with metastatic melanoma, metastatic non-small cell lung cancer, recurrent or metastatic head and neck cancer, refractory classical Hodgkin lymphoma, and urothelial carcinoma.

Safety and efficacy of pembrolizumab for this indication were studied in patients with MSI-H or dMMR solid tumors who were enrolled in one of five uncontrolled, single-arm clinical trials. In some trials, patients were required to have MSI-H or dMMR cancers, while in other trials, a subgroup of patients were identified as having MSI-H or dMMR cancers by testing tumor samples after treatment began.

A total of 15 cancer types were identified among 149 patients enrolled across these five clinical trials. The

(Keytruda—Merck)

FDA approves first cancer treatment for any solid tumor with a specific biomarker

most common cancers were colorectal, endometrial, and other gastrointestinal cancers. Approval for this indication was based on the percentage of patients who experienced complete or partial shrinkage of their tumors (overall response rate) and for how long (durability of response). Of the 149 patients who received pembrolizumab in the trials, 39.6% had a complete or partial response. For 78% of those patients, the response lasted for 6 months or more.

Common adverse effects include fatigue, pruritus, diarrhea, decreased appetite, rash, fever, cough, difficulty breathing, musculoskeletal pain, constipation, and nausea.

Pembrolizumab can cause serious conditions, known as immune-mediated adverse effects, including inflammation of healthy organs such as the lungs (pneumonitis), colon (colitis), liver (hepatitis), endocrine glands (endocrinopathies), and kidneys (nephritis). Complications or death related to allogeneic hematopoietic stem cell transplantation after using pembrolizumab has occurred.

Patients who experience severe or life-threatening infusion-related reactions should stop taking pembrolizumab. Women who are pregnant or breastfeeding should not take pembrolizumab because it may cause harm to a developing fetus or newborn baby.

Safety and effectiveness of the agent in pediatric patients with MSI-H central nervous system cancers have not been established.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/fda-approves-first-cancer-treatment-any-solid-tumor-specific-biomarker>

Supplemental Approvals

Generic Name (Trade Name—Company)

June 14, 2018

Bevacizumab

Uses/Notes

FDA approved [bevacizumab](#) for patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with carboplatin and paclitaxel, followed by single-agent bevacizumab, for Stage III or IV disease after initial surgical resection.

Approval was based on a multicenter, randomized, double-blind, placebo-controlled, three-arm study evaluating the addition of bevacizumab to carboplatin and paclitaxel for patients with Stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection.

A total of 1,873 patients were randomized to carboplatin plus paclitaxel without bevacizumab, carboplatin plus paclitaxel with bevacizumab for up to six cycles, or carboplatin plus paclitaxel with bevacizumab for six cycles followed by single-agent bevacizumab for up to 16 additional doses. Bevacizumab was administered at 15 mg/kg intravenously every 3 weeks. On this trial, 1,215 patients received at least one bevacizumab dose.

The primary efficacy outcome was investigator-assessed progression-free survival (PFS); overall survival (OS) was a secondary outcome. The estimated median PFS was 18.2 months for patients receiving bevacizumab with chemotherapy followed by single-agent bevacizumab (hazard ratio [HR] 0.62 [95% CI 0.52–0.75]; $P < 0.0001$). For those receiving bevacizumab with chemotherapy without single-agent bevacizumab, the estimated median PFS was 12.8 months (HR 0.83 [95% CI 0.70–0.98]; not significant).

For patients receiving chemotherapy without bevacizumab, the estimated median PFS was 12.0 months. Estimated median OS was 43.8 months in the bevacizumab with chemotherapy followed by bevacizumab, compared with 40.6 months in the chemotherapy alone arm (HR 0.89 [95% CI 0.76–1.05]).

Adverse reactions occurring at higher incidence (at least 5%) of patients receiving bevacizumab were diarrhea, nausea, stomatitis, fatigue, arthralgia, muscular weakness, pain in extremity, dysarthria, headache,

(Avastin—Genentech)

Bevacizumab now approved in combination with chemotherapy for ovarian cancer

dyspnea, epistaxis, nasal mucosal disorder, and hypertension.

Grade 3-4 adverse reactions occurring at a higher incidence (??%) in either of the bevacizumab arms versus the control arm were fatigue, hypertension, decreased platelet count, and decreased white blood cell count.

The recommended bevacizumab dose for Stage III or IV epithelial ovarian, fallopian tube, or primary peritoneal cancer following initial surgical resection is 15 mg/kg every 3 weeks with carboplatin and paclitaxel for up to six cycles, followed by 15 mg/kg every 3 weeks as a single agent, for a total of up to 22 cycles.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/bevacizumab-now-approved-combination-chemotherapy-ovarian-cancer>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

June 15, 2018

Buprenorphine and naloxone

Uses/Notes

FDA approved the [first generic versions](#) of Suboxone (buprenorphine and naloxone) sublingual film for the treatment of opioid dependence.

[Medication-assisted treatment \(MAT\)](#) is a comprehensive approach that combines FDA-approved medications (currently methadone, buprenorphine, or naltrexone) with counseling and other behavioral therapies to treat patients with opioid use disorder (OUD). Regular adherence to MAT with buprenorphine reduces opioid withdrawal symptoms and the desire to use opioids, without causing the cycle of highs and lows associated with opioid misuse or abuse.

At proper doses, buprenorphine also decreases the pleasurable effects of other opioids, making continued opioid abuse less attractive. According to the Substance Abuse and Mental Health Services Administration, patients receiving MAT for treatment of their OUD cut their risk of death from all causes in half.

One of the ways FDA is encouraging access and wider use of MAT is through the approval of generic versions of these products. Generic drugs approved by FDA have, among other things, the same quality as brand-name drugs. Generic drug manufacturing and packaging sites must meet the same quality standards as those of brand-name drugs.

Adverse events commonly observed with the buprenorphine and naloxone sublingual film are oral hypoesthesia (numbness), glossodynia (burning mouth), oral mucosal erythema (inflammation of oral mucous membrane), headache, nausea, vomiting, hyperhidrosis (excessive sweating), constipation, signs and symptoms of withdrawal, insomnia, pain, and peripheral edema (accumulation of fluid causing swelling in lower limbs). These products may only be prescribed by Drug Addiction Treatment Act (DATA)-certified prescribers.

Mylan Technologies and Dr. Reddy's Laboratories received approval to market buprenorphine and naloxone sublingual film in multiple strengths. Buprenorphine and naloxone sublingual film should be

(Suboxone—Mylan Technologies, Dr. Reddy's Laboratories)

used as part of a complete treatment plan that includes counseling and psychosocial support.

FDA approves first generic versions of sublingual film to treat opioid dependence

Source URL:

<http://www.aphadruonline.com/supplemental-approvals/fda-approves-first-generic-versions-sublingual-film-treat-opioid-dependence>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

June 15, 2018

Moxidectin

(No trade name—Medicines Development for Global Health)

Medication treats river blindness in patients aged 12 years and older

Uses/Notes

FDA has approved moxidectin 8-mg tablets to treat river blindness ([onchocerciasis](#)) in patients aged 12 years and older. FDA has also awarded a priority review voucher (PRV) to the manufacturer, Medicines Development for Global Health (MDGH).

River blindness is caused by a parasitic worm, *Onchocerca volvulus*. The disease manifests as severe itching, disfiguring skin conditions, and visual impairment, including permanent blindness, caused by the worm's larvae (microfilariae).

Approval of moxidectin was based on data from two randomized, double-blind, active controlled clinical studies. Each study met its respective primary endpoints, showing a statistically significant superiority of moxidectin over the current standard of care, ivermectin, in suppressing the presence of the microfilariae in skin. Full results from the Phase III study were published in the [Lancet](#) in January 2018.

Moxidectin is supplied as 2-mg tablets for administration as an 8-mg dose per oral to patients at least 12 years of age with *O. volvulus* infection.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/medication-treats-river-blindness-patients-aged-12-years-and-older>

[Alerts and Recalls](#)

Generic Name (Trade Name—Company)

June 15, 2018

Triamcinolone and moxifloxacin

(No trade names—Guardian Pharmacy Services)

FDA warns of adverse events from compounded product for intravitreal injection

Uses/Notes

FDA is [alerting](#) health professionals of adverse events associated with a drug containing triamcinolone (a steroid) and moxifloxacin (anti-infective) compounded by Guardian Pharmacy Services in Dallas. FDA received adverse event reports on April 5 and June 1, 2017, and conducted follow-up concerning at least 43 patients who were administered intravitreal (eye) injections of the drug at the end of a cataract surgery procedure at the PRG Dallas Ambulatory Surgery Center.

The purpose of the injection was to provide postoperative prophylaxis for ocular inflammation and endophthalmitis with the expectation that the patient would not need to use postoperative eye drops.

Over the course of several months, patients developed various symptoms, including vision impairment (blurred or decreased vision), poor night vision, loss of color perception, photophobia (light sensitivity), glare, halos, flashing lights, ocular discomfort, pain, loss of balance, headaches, and/or nausea. A number of the symptoms were not exhibited until at least 1 month postoperatively.

During follow-up examinations, physicians observed that the patients had diminished visual function involving both visual acuity and visual fields. Optical coherence tomography testing initially showed macular edema, which was followed in some cases by retinal degeneration. While the symptoms reportedly improved in some patients over the 5-month postoperative period, a number of patients remain with a significant reduction in best-corrected visual acuity and visual fields.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/fda-warns-adverse-events-compounded-product-intravitreal-injection>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

June 19, 2018

Pembrolizumab

(*Keytruda—Merck*)

New indication for treatment of refractory or relapsed PMBCL

Uses/Notes

[Merck announced](#) FDA approval of pembrolizumab to treat adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (PMBCL) or relapsed PMBCL after two or more prior lines of therapy. With this indication, pembrolizumab becomes the first anti-PD-1 therapy to be approved for treatment of PMBCL, a type of non-Hodgkin lymphoma. It is the second indication for the agent for treatment of a hematologic malignancy.

This indication was approved under the FDA's accelerated approval regulations based on tumor response rate and durability of response.

The agent is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Immune-mediated adverse reactions include pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, severe skin reactions and solid organ transplant rejection. Because of the severity of the adverse reaction, pembrolizumab should be withheld or discontinued and corticosteroids administered if appropriate. Immune-mediated complications, including fatal events, occurred in patients with classical Hodgkin lymphoma who underwent allogeneic hematopoietic stem cell transplantation after treatment with pembrolizumab.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/new-indication-treatment-refractory-or-relapsed-pmbcl>

New Drug Approvals

Generic Name (Trade Name—Company)

June 25, 2018

Cannabidiol

Uses/Notes

[FDA has approved cannabidiol](#) (CBD) oral solution under the trade name Epidiolex to treat seizures associated with two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in patients aged 2 years and older. This is the first FDA-approved drug that contains a purified drug substance derived from marijuana. It is also the first FDA approval of a drug for to treat patients with Dravet syndrome.

CBD is a chemical component of the Cannabis sativa plant, more commonly known as marijuana. However, CBD does not cause intoxication or euphoria (the “high”) that comes from tetrahydrocannabinol (THC).

It is THC (and not CBD) that is the primary psychoactive component of marijuana.

Dravet syndrome is a rare genetic condition that appears during the first year of life with frequent fever-related seizures. Later, other types of seizures typically arise, including myoclonic seizures (involuntary muscle spasms). 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.

Lennox-Gastaut syndrome begins in childhood. It is characterized by multiple types of seizures. People with Lennox-Gastaut syndrome begin having frequent seizures in early childhood, usually between ages 3 and 5. More than three-quarters of affected individuals have tonic seizures, which cause the muscles to contract uncontrollably. Almost all children with Lennox-Gastaut syndrome develop learning problems and intellectual disability. Many also have delayed development of motor skills such as sitting and crawling. Most people with Lennox-Gastaut syndrome require help with usual activities of daily living.

Epidiolex’s effectiveness was studied in three randomized, double-blind, placebo-controlled clinical

(Epidiolex—GW Research Ltd.)

FDA approves first drug containing cannabidiol to treat severe epilepsy

trials involving 516 patients with either Lennox-Gastaut syndrome or Dravet syndrome. Epidiolex, taken along with other medications, was shown to be effective in reducing the frequency of seizures when compared with placebo.

The most common adverse effects that occurred in Epidiolex-treated patients in the clinical trials were: sleepiness, sedation and lethargy; elevated liver enzymes; decreased appetite; diarrhea; rash; fatigue, malaise and weakness; insomnia, sleep disorder and poor quality sleep; and infections.

Epidiolex must be dispensed with a patient Medication Guide that describes important information about the drug's uses and risks. As is true for all 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. Epidiolex also caused liver injury, generally mild, but raising the possibility of rare but more severe injury. More severe liver injury can cause nausea, vomiting, abdominal pain, fatigue, anorexia, jaundice, and/or dark urine.

Under the Controlled Substances Act (CSA), CBD is currently a Schedule I substance because it is a chemical component of the cannabis plant. In support of this application, the company conducted nonclinical and clinical studies to assess the abuse potential of CBD.

FDA prepares and transmits, through the U.S. Department of Health and Human Services, a medical and scientific analysis of substances subject to scheduling, like CBD, and provides recommendations to the Drug Enforcement Administration (DEA) regarding controls under the CSA. DEA is required to make a scheduling determination.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-first-drug-containing-cannabidiol-treat-severe-epilepsy>

Alerts and Recalls

Generic Name (Trade Name—Company)

June 25, 2018

Pembrolizumab, atezolizumab

(Keytruda, Tecentriq—Merck, Genentech)

FDA restricts use of agents because of efficacy concerns

Uses/Notes

[FDA is restricting](#) the use of pembrolizumab and atezolizumab for patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing therapy.

These changes are the result of decreased survival associated with the use of pembrolizumab or atezolizumab as single therapy compared with platinum-based chemotherapy in clinical trials to treat patients with metastatic urothelial cancer who have not received prior therapy and who have low expression of the protein programmed death ligand 1 (PD-L1).

The labels of both drugs have been revised to reflect the restricted indications.

The tests used in the trial to determine PD-L1 expression are listed in Section 14 of each label.

FDA is reviewing the findings of ongoing analyses and will communicate new information about the PD-L1 assays and indications as it becomes available.

In patients already receiving pembrolizumab or atezolizumab who are responding to treatment and are cisplatin ineligible, continuation of treatment could be considered, regardless of PD-L1 status. FDA has not changed the indications of pembrolizumab or atezolizumab for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment.

Patients taking pembrolizumab or atezolizumab for other approved uses should continue to take their medication as directed by their health professional.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/fda-restricts-use-agents-because-efficacy-concerns>

Supplemental Approvals

Generic Name (Trade Name—Company)

June 25, 2018

Isoproterenol hydrochloride injection

(No trade name—Amphastar)

Amphastar announces FDA approval of generic isoproterenol hydrochloride injection

Uses/Notes

[Amphastar announced FDA approval](#) of isoproterenol hydrochloride injection, USP 0.2 mg/mL, 1mL and 0.2 mg/mL, 5-mL single-dose vial, for multiple uses including mild or transient episodes of heart block that do not require electric shock or pacemaker therapy.

The product was determined by FDA to be therapeutically equivalent to Isuprel, which is sold in the United States by Valeant Pharmaceuticals.

Amphastar anticipates launching the product in the third quarter of 2018.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/amphastar-announces-fda-approval-generic-isoproterenol-hydrochloride>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

June 25, 2018

Insulin delivery and monitoring device

(MiniMed 670G hybrid closed looped system—Medtronic)

Automated insulin delivery and monitoring system approved for younger pediatric patients

Uses/Notes

[FDA has expanded](#) the approval of the MiniMed 670G hybrid closed looped system, a diabetes management device that is intended to automatically monitor glucose and provide appropriate basal insulin doses with little or no input from the user, to include individuals aged 7 to 13 with type 1 diabetes.

FDA originally approved this device in September 2017 for use in patients aged 14 years and older with type 1 diabetes. The device works by measuring glucose levels every 5 minutes and automatically adjusting insulin delivery by either administering or withholding insulin.

The system includes a sensor that attaches to the body to measure glucose levels under the skin, an insulin pump strapped to the body, and an infusion patch connected to the pump with a catheter that delivers insulin. While the device automatically adjusts insulin levels, users need to manually request insulin doses to counter carbohydrate consumption at mealtime.

Approval was based on data from a clinical trial that included 105 individuals aged 7 to 11 years. Study participants wore the device for approximately 3.5 months and participated in three phases of the study to evaluate both at-home use as well as remote use. That study found no serious adverse events associated with use of the MiniMed 670G and that the device is safe for use in people aged 7 to 13 years with type 1 diabetes.

Risks associated with use of the system may include hypoglycemia, hyperglycemia, as well as skin irritation or redness around the device's infusion patch.

As part of this approval, FDA is requiring a postmarketing study to evaluate device performance in real-world settings in children between the ages of 7 and 13. This device is not approved for use in children aged 6 years or younger or in individuals who require less than eight units of insulin per day.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/automated-insulin-delivery-and-monitoring-system-approved->

younger-pediatric

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

June 25, 2018

Desmopressin acetate

(Nocturna—Ferring Pharmaceuticals)

First sublingual tablet approved to treat nocturia due to nocturnal polyuria

Uses/Notes

FDA approved [desmopressin acetate](#) as the first sublingual tablet for treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to void. The formulation of the sublingual tablet and sex-specific dosing was demonstrated to be effective in reducing nighttime trips to the bathroom in adults aged 18 years and older.

Nocturnal polyuria, a disease of the kidneys, is the most common underlying cause of nocturia, which can affect adults at every age. It occurs when a person has insufficient nocturnal vasopressin, causing an overproduction of urine in the kidneys at night. Unlike treatments that target the bladder or prostate, desmopressin acetate acts on receptors in the kidney to absorb more fluid and produce less urine during the night while patients sleep.

The product was approved with a boxed warning because it can cause hyponatremia. Severe hyponatremia can be life threatening, leading to seizures, coma, respiratory arrest, or death.

Desmopressin acetate will be available in the second half of 2018.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/first-sublingual-tablet-approved-treat-nocturia-due-nocturnal-polyuria>

Supplemental Approvals

Generic Name (Trade Name—Company)

June 25, 2018

C1 esterase inhibitor (human)

(Cinryze—Shire)

Approval expanded to prevent angioedema attacks in children aged 6 years and older with HAE

Uses/Notes

[Shire announced FDA approval](#) of an expanded indication for C1 esterase inhibitor (human) to prevent angioedema attacks in children aged 6 years and older with hereditary angioedema (HAE). The product has been approved in the U.S. since October 2008 for routine prophylaxis against attacks in adolescents and adults living with HAE.

HAE is a rare, genetic disorder estimated to affect about 1 in 10,000 to 1 in 50,000 people worldwide. The condition results in recurring attacks of edema in various parts of the body, including the abdomen, face, feet, genitals, hands, and throat. The attacks can be debilitating and painful, with those that obstruct the airways potentially life threatening because of the risk of asphyxiation.

The agent is contraindicated in patients who have had life-threatening, immediate hypersensitivity reactions, including anaphylaxis, after using it.

Health professionals are urged to consider treatment methods carefully because hypersensitivity reactions may have symptoms similar to HAE attacks. If an acute severe hypersensitivity reaction occurs, infusion of the product should be discontinued and epinephrine administered.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/approval-expanded-prevent-angioedema-attacks-children-aged-6-years-and-older>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

June 27, 2018

Plazomicin

Uses/Notes

Achaogen announced [FDA approval of plazomicin](#), an I.V. infusion administered once daily, for adults aged 18 years and older with complicated urinary tract infections (cUTI), including pyelonephritis, caused by Enterobacteriaceae bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Enterobacter cloacae*). The drug is for patients who have limited or no alternative treatment options.

Plazomicin was engineered to overcome aminoglycoside-modifying enzymes, the most common aminoglycoside-resistance mechanism in Enterobacteriaceae, and has in vitro activity against extended-spectrum beta-lactamase (ESBL)-producing, aminoglycoside-resistant, and carbapenem-resistant isolates.

CDC has characterized ESBL-producing Enterobacteriaceae as a “serious threat” and CRE as “nightmare bacteria”—immediate public health threats that require urgent and aggressive action.

Approval was supported in part by data from the EPIC (Evaluating Plazomicin In cUTI) clinical trial, the first randomized controlled study of once-daily aminoglycoside therapy for treatment of cUTI, including pyelonephritis.

As only limited clinical safety and efficacy data for plazomicin are currently available, plazomicin is reserved for use in cUTI patients who have limited or no alternative treatment options.

To reduce the development of drug-resistant bacteria and maintain effectiveness of plazomicin and other antibacterial drugs, plazomicin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible microorganisms.

On the potential indication for plazomicin to treat bloodstream infection (BSI), FDA issued a Complete Response Letter (CRL) stating that the CARE study does not provide substantial evidence of effectiveness of

(Zemdri—Achaogen)

New drug targets complicated urinary tract infections in adults

plazomicin for this indication. The company intends to meet with FDA to determine whether there is a feasible resolution to address the CRL.

Achaogen will work with hospitals, providers, and insurers to ensure patients are able to receive this treatment. Patients, physicians, pharmacists, or other health professionals with questions about plazomicin should contact 1-833-252-6400 or visit www.ZEMDRI.com.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/new-drug-targets-complicated-urinary-tract-infections-adults>

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