
A^{PhA} **DrugInfoLine[®]**

May 2018

[Focus on Asthma Care](#)

Advising on this article: Devra K. Dang

May 1, 2018

Increasing inhaled glucocorticoid doses to prevent asthma exacerbations

Key Point

In children with moderate to severe persistent asthma, quintupling the inhaled corticosteroid (ICS) dose at early signs of loss of asthma control did not reduce the rate of severe asthma exacerbations; however, in adolescents and adults, quadrupling the ICS dose when asthma control started to deteriorate did result in fewer severe exacerbations in a small group of patients, according to two studies published in the New England Journal of Medicine.

Source URL:

<http://www.aphadruginfoline.com/focus-asthma-care/increasing-inhaled-glucocorticoid-doses-prevent-asthma-exacerbations>

[Respiratory](#)

Advising on this article: Roy A. Pleasants, II

May 1, 2018

Nebulized glycopyrrolate improved outcomes in patients with COPD

Key Point

Data from two Phase III trials showed that the SUN-101/eFlow product (Lonhala Magnair—Sunovion)—nebulized glycopyrrolate delivered through an electronic device—was well tolerated and resulted in improved lung function and patient-reported outcomes (PROs) in individuals with moderate to very severe chronic obstructive pulmonary disorder (COPD).

Source URL:

<http://www.aphadruginfoline.com/respiratory/nebulized-glycopyrrolate-improved-outcomes-patients-copd>

Cardiology

Advising on this article: Eric MacLaughlin

May 7, 2018

Pharmacist interventions at black barbershops effective at reducing BP

Key Point

Pharmacist-led interventions in black barbershops resulted in significantly greater blood pressure (BP) reductions in patrons with uncontrolled hypertension (HTN) compared with an intervention that focused on barbers encouraging their patrons to make healthy lifestyle modifications and see their doctors, according to results of a trial published in the New England Journal of Medicine.

Source URL:

<http://www.aphadruginfoline.com/cardiology/pharmacist-interventions-black-barbershops-effective-reducing-bp>

[Nephrology](#)

Advising on this article: Edward F. Foote

May 7, 2018

Balanced crystalloids may be preferred to I.V. saline

Key Point

Two large, single-center trials published in the *New England Journal of Medicine* comparing balanced crystalloid solutions with saline in both noncritically ill and critically ill adults found that use of balanced crystalloid solutions resulted in significant reductions in the risk of major adverse kidney events within 30 days (defined as a composite of death from any cause, use of new renal-replacement therapy, or persistent renal dysfunction).

Source URL:

<http://www.aphadruginfoline.com/nephrology/balanced-crystalloids-may-be-preferred-iv-saline>

[Drug Interactions Corner](#)

Advising on this article: Daniel S. Streetman

May 14, 2018

Common antibiotics do not appear to interact with hormonal contraceptives

Key Point

Clinical and pharmacokinetic studies do not appear to support an interaction between hormonal contraceptives (HCs) and most nonrifamycin antibiotics (e.g., penicillins/cephalosporins, tetracyclines, fluoroquinolones, macrolides, and others), according to results of a systematic review of 29 studies published in the American Journal of Obstetrics and Gynecology.

Source URL:

<http://www.aphadruginfoline.com/drug-interactions-corner/common-antibiotics-do-not-appear-interact-hormonal-contraceptives>

[Infectious Diseases](#)

Advising on this article: Allana Sucher

May 14, 2018

Inappropriate use of antibiotics for acute sinusitis

Key Point

An observational study published in JAMA Internal Medicine that assessed more than 3 million physician office visits for acute sinusitis showed that more than two-thirds of prescribed antibiotics were given for 10 days or longer, despite current guidelines recommending a treatment duration of 5 to 7 days for uncomplicated cases in adult patients.

Source URL:

<http://www.aphadruginfo.com/infectious-diseases/inappropriate-use-antibiotics-acute-sinusitis>

[Rheumatology](#)

Advising on this article: Arthur A. Schuna

May 21, 2018

Temporary stopping MTX improves immunogenicity of influenza vaccination

Key Point

In patients with rheumatoid arthritis (RA), holding the methotrexate (MTX) dose for 2 weeks after administration of the seasonal influenza vaccine improved vaccine response compared with patients who continued MTX treatment, according to results of a randomized trial published in BMJ.

Source URL:

<http://www.aphadruginfoline.com/rheumatology/temporary-stopping-mtx-improves-immunogenicity-influenza-vaccination>

[Endocrinology](#)

Advising on this article: Frank Pucino

May 21, 2018

Efficacy of common treatments for vulvovaginal symptoms

Key Point

Use of vaginal estradiol tablets or OTC vaginal moisturizer was no more effective than placebo tablets and gel at reducing vulvovaginal symptoms in postmenopausal women, according to results of a 12-week trial published in JAMA Internal Medicine.

Source URL:

<http://www.aphadruonline.com/endocrinology/efficacy-common-treatments-vulvovaginal-symptoms>

Alerts and Recalls

Generic Name (Trade Name—Company)

May 1, 2018

Lamotrigine

Uses/Notes

[FDA warned](#) that use of lamotrigine for seizures and bipolar disorder can cause a rare but very serious reaction that excessively activates the body's immune system. This can cause severe inflammation throughout the body and lead to hospitalization and death, especially if the reaction is not diagnosed and treated quickly. As a result, FDA is requiring a new warning that this risk be added to the prescribing information in the lamotrigine drug labels.

The immune system reaction, called hemophagocytic lymphohistiocytosis (HLH), typically presents as a persistent fever, usually greater than 101°F. HLH can lead to severe problems with blood cells and organs throughout the body, such as the liver, kidneys, and lungs.

Lamotrigine is used alone or with other medications to treat seizures in patients aged 2 years and older. It may also be used as maintenance treatment in patients with bipolar disorder.

Health professionals should be aware that prompt recognition and early treatment is important for improving HLH outcomes and decreasing mortality. Diagnosis is often complicated, as early signs and symptoms such as fever and rash are not specific.

HLH may also be confused with other serious immune-related adverse reactions. Evaluate patients who develop fever or rash promptly, and discontinue lamotrigine if HLH or another serious immune-related adverse reaction is suspected and an alternative etiology for the signs and symptoms cannot be established.

Since lamotrigine's 1994 approval, FDA identified eight cases worldwide of confirmed or suspected HLH associated with the medication in children and adults. This number includes only reports submitted to FDA and found in the medical literature, so there are likely additional cases about FDA is unaware, according to the agency. FDA determined there was reasonable evidence that lamotrigine was the cause of HLH in these

(Lamictal—GlaxoSmithKline)

FDA warns of serious immune system reaction with use of lamotrigine

eight cases based on the timing of events and order in which they occurred. These patients required hospitalization and received drug and other medical treatments, with one dying.

A link to the full communication detailing specific information for health professionals and the complete Data Summary can be found at www.fda.gov/DrugSafetyCommunications.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/fda-warns-serious-immune-system-reaction-use-lamotrigine>

Supplemental Approvals

Generic Name (Trade Name—Company)

May 1, 2018

Dabrafenib, trametinib

Uses/Notes

[FDA granted regular approval](#) to dabrafenib and trametinib in combination for the adjuvant treatment of patients with melanoma with *BRAF V600E* or *V600K* mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection.

Approval was based on COMBI-AD, an international, multicenter, randomized, double-blind, placebo-controlled trial in 870 patients with Stage III melanoma with *BRAF V600E* or *V600K* mutations, and pathologic involvement of regional lymph node(s). Patients were randomly allocated (1:1) to receive dabrafenib 150 mg twice daily in combination with trametinib 2 mg once daily or two placebos for up to 1 year.

The major efficacy outcome was relapse-free survival (RFS). RFS was defined as the time from randomization to disease recurrence (local, regional, or distant metastasis), new primary melanoma, or death from any cause, whichever occurred first as assessed by the investigator.

Patients who received the combination treatment had a statistically significant improvement in RFS compared with those receiving placebo. Patients in the combination arm experienced fewer recurrences/deaths at the time of data cutoff: 38% (n = 166), compared with 57% (n = 248) in the placebo arm (hazard ratio 0.47 [95% CI 0.39–0.58]; $P < 0.0001$). The estimated median RFS was not reached for patients who received the combination therapy, compared with 16.6 months (95% CI 12.7–22.1) for those receiving placebo.

The most common adverse reactions in at least 20% of patients were pyrexia, fatigue, nausea, headache, rash, chills, diarrhea, vomiting, arthralgia, and myalgia.

Adverse reactions resulting in discontinuation, dose reduction, or dose interruption of dabrafenib occurred in 25%, 35%, and 66% of patients, respectively; the most common for each were pyrexia and chills.

(Tafinlar, Mekinist—Novartis)

Dabrafenib plus trametinib approved for adjuvant treatment of melanoma with BRAF V600E or V600K mutations

Adverse reactions resulting in discontinuation and dose interruption of trametinib occurred in 24% and 54% of patients respectively; the most common for each were pyrexia and chills.

Adverse reactions leading to dose reduction of trametinib occurred in 23% of patients; the most common were pyrexia and decreased ejection fraction.

The recommended doses for adjuvant treatment of melanoma are 150 mg of dabrafenib orally twice daily and 2 mg of trametinib orally once daily until disease recurrence or unacceptable toxicity, for up to 1 year.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/dabrafenib-plus-trametinib-approved-adjuvant-treatment-melanoma-braf-v600e-or>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

May 1, 2018

Tolvaptan

(Jynarque—Otsuka)

Agent slows kidney function decline in adults at risk of rapidly progressing ADPKD

Uses/Notes

FDA has approved [tolvaptan](#) as the first drug treatment to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD), a genetic disease with consequences that can lead to dialysis or kidney transplantation.

ADPKD is a progressively debilitating and often painful disorder in which fluid-filled cysts develop in the kidneys over time. These cysts enlarge the kidneys and impair their ability to function normally, leading to kidney failure in most patients.

ADPKD is diagnosed in approximately 140,000 people in the United States and affects families across multiple generations, since a parent with ADPKD has a 50% chance of passing the disease on to each of their children.

Tolvaptan can cause serious and potentially fatal liver injury, and acute liver failure requiring liver transplantation has been reported. Tolvaptan has been associated with ALT and AST elevations, with infrequent cases of concomitant elevations in bilirubin-total.

To ensure the safety of patients taking tolvaptan, it is necessary to measure ALT, AST, and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then monthly for 18 months and every 3 months thereafter, for as long as the patient is on tolvaptan treatment.

Because of the risks of serious liver injury, tolvaptan is available only through a restricted distribution program supported by a Risk Evaluation and Mitigation Strategy program approved by FDA.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/agent-slows-kidney-function-decline-adults-risk-rapidly-progressing-adpkd>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

May 7, 2018

Dabrafenib, trametinib

Uses/Notes

FDA [approved dabrafenib and trametinib](#), administered together, for treatment of anaplastic thyroid cancer (ATC) that cannot be removed by surgery or is metastatic and that is mutation positive for the *BRAF V600E* gene.

It is the first FDA-approved treatment for patients with this aggressive form of thyroid cancer, and the third cancer with this specific gene mutation that this drug combination has been approved to treat.

Both dabrafenib and trametinib are also approved for use, alone or in combination, to treat *BRAF V600* mutation-positive metastatic melanoma, and for use, in combination, to treat *BRAF V600E* mutation-positive, metastatic non-small cell lung cancer.

Efficacy of dabrafenib and trametinib in treating ATC was shown in an open-label clinical trial of patients with rare cancers with the *BRAF V600E* mutation. Data from trials in *BRAF V600E* mutation-positive, metastatic melanoma or lung cancer and results in other *BRAF V600E* mutation-positive rare cancers provided confidence in the results seen in patients with ATC.

The trial measured the percent of patients with a complete or partial reduction in tumor size (overall response rate). Of 23 evaluable patients, 57% experienced a partial response, and 4% experienced a complete response; in 9 (64%) of the 14 patients with responses, there were no significant tumor growths for 6 months or longer.

Adverse effects in patients with ATC are consistent with those seen in other cancers when the two drugs are used together. Common adverse effects include fever, rash, chills, headache, joint pain, cough, fatigue, nausea, vomiting, diarrhea, myalgia, dry skin, decreased appetite, edema, hemorrhage, hypertension, and difficulty breathing.

Adverse effects of dabrafenib include the development of new cancers, growth of tumors in patients with *BRAF* wild-type tumors, serious bleeding problems, heart

(Tafinlar, Mekinist—Novartis)

FDA approves new uses for two drugs administered together for treatment of BRAF-positive anaplastic thyroid cancer

problems, severe eye problems, fever that may be severe, serious skin reactions, high blood glucose levels or worsening diabetes, and serious anemia.

Severe adverse effects of trametinib include the development of new cancers; serious bleeding problems; inflammation of intestines and perforation of the intestines; blood clots in the arms, legs or lungs; heart problems; severe eye problems; lung or breathing problems; fever that may be severe; serious skin reactions; and high blood glucose levels or worsening diabetes.

Both drugs can cause harm to a developing fetus; women should be advised of the potential risk to the fetus and to use effective contraception.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/fda-approves-new-uses-two-drugs-administered-together-treatment-braf-positive>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

May 7, 2018

Tisagenlecleucel

(Kymriah—Novartis)

Agent receives second FDA approval to refractory or relapsed large B-cell lymphoma

Uses/Notes

FDA has approved [tisagenlecleucel suspension](#) for I.V. infusion for its second indication—treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. It is not indicated for treatment of patients with primary central nervous system lymphoma.

The agent was the first chimeric antigen receptor T cell (CAR-T) therapy to receive regulatory approval in August 2017 to treat patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Tisagenlecleucel is now the only CAR-T cell therapy to receive FDA approval for two distinct indications in non-Hodgkin lymphoma (NHL) and B-cell ALL

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/agent-receives-second-fda-approval-refractory-or-relapsed-large-b-cell>

Supplemental Approvals

Generic Name (Trade Name—Company)

May 7, 2018

Tisagenlecleucel

(Kymriah—Novartis)

Agent receives second FDA approval for treatment of refractory or relapsed large B-cell lymphoma

Uses/Notes

FDA has approved [tisagenlecleucel suspension](#) for I.V. infusion for its second indication—treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. It is not indicated for treatment of patients with primary central nervous system lymphoma.

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Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/agent-receives-second-fda-approval-treatment-refractory-or-relapsed-large-b>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

May 7, 2018

Coagulation factor Xa (recombinant), inactivated-zhzo

(*Andexxa—Portola*)

FDA approves first and only antidote for reversal of Factor Xa inhibitors

Uses/Notes

FDA has [approved](#) coagulation factor Xa (recombinant), inactivated-zhzo, the first and only antidote indicated for patients treated with rivaroxaban and apixaban, when reversal of anticoagulation is needed because of life-threatening or uncontrolled bleeding.

The agent is a recombinant protein specifically designed to bind to Factor Xa inhibitors and rapidly reverse their anticoagulant effect. A modified form of the human Factor Xa molecule, it works by acting as a decoy for oral and injectable Factor Xa inhibitors, which target and bind to Factor Xa, which allows them to exert their anticoagulant effect. When the agent is given to a patient with Factor Xa inhibitor-related bleeding, it binds to the Factor Xa inhibitor and prevents it from inhibiting the activity of Factor Xa and reverses the anticoagulant effects of the inhibitor.

Approval was supported by data from two Phase III ANNEXA studies (ANNEXA-R and ANNEXA-A) that evaluated its safety and efficacy in reversing the anticoagulant activity of the Factor Xa inhibitors rivaroxaban and apixaban in healthy volunteers. Results demonstrated that the agent rapidly and significantly reversed anti-Factor Xa activity. The median decrease in anti-Factor Xa activity from baseline was 97% for rivaroxaban and 92% for apixaban.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-first-and-only-antidote-reversal-factor-xa-inhibitors>

[Alerts and Recalls](#)

Generic Name (Trade Name—Company)

May 14, 2018

Piperacillin and tazobactam for injection, 3.375 g vials

(No trade name—AuroMedics Pharma)

Recalled product contains glass particulate matter

Uses/Notes

AuroMedics Pharma is voluntarily [recalling](#) two lots (PP0317061-A, exp. Aug 2019, and PP0317049-A, exp. Aug 2019) of piperacillin and tazobactam for injection, 3.375 g (piperacillin sodium equivalent to 3 g of piperacillin and tazobactam sodium equivalent to 0.375 g of tazobactam) to the hospital level. Each single-dose vial contains 7.05 mEq (162 mg) of sodium.

The medication is packaged in a carton containing 10 single-dose vials (NDC: 55150-120-30).

The products have been found to contain particulate matter, visible only after reconstitution, that was confirmed to be glass within the vial.

Administration of a glass particulate, if present in I.V. drug, may result in local irritation or swelling in response to the foreign material. More serious potential outcomes would include blockage and clotting in blood vessels, which may be life-threatening.

Piperacillin and tazobactam for injection is used for treatment of patients with moderate to severe infections caused by susceptible isolates of the designated bacteria in intra-abdominal, skin and skin structure, and female pelvic infections, as well as community acquired and nosocomial pneumonia.

AuroMedics Pharma is notifying its distributors and customers by recall letters and is arranging for return and replacement of all recalled product.

To date, AuroMedics Pharma has not received reports of any adverse events or identifiable safety concerns attributed to use of the product from these lots.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/recalled-product-contains-glass-particulate-matter>

Supplemental Approvals

Generic Name (Trade Name—Company)

May 14, 2018

Fingolimod

Uses/Notes

FDA approved [fingolimod](#) to treat relapsing multiple sclerosis (MS) in children and adolescents aged 10 years and older. This is the first FDA approval of a drug to treat MS in pediatric patients.

Fingolimod was first approved by FDA in 2010 to treat adults with relapsing MS.

Approval was based on a clinical trial evaluating the effectiveness of fingolimod in treating 214 patients aged 10 to 17 with MS. The trial compared fingolimod with another MS drug, interferon beta-1a.

In the study, 86% of patients receiving fingolimod remained relapse-free after 24 months of treatment, compared with 46% of those receiving interferon beta-1a.

Adverse effects of fingolimod in pediatric trial participants were similar to those seen in adults. The most common adverse effects were headache, liver enzyme elevation, diarrhea, cough, flu, sinusitis, back pain, abdominal pain, and pain in extremities.

Fingolimod must be dispensed with a patient Medication Guide explaining serious risks, including slowing of the heart rate, especially after the first dose. Fingolimod may increase the risk of serious infections. Patients should be monitored for infection during treatment and for 2 months after treatment is discontinued.

Progressive multifocal leukoencephalopathy (PML), a rare brain infection that usually leads to death or severe disability, has been reported in patients being treated with fingolimod. PML cases usually occur in patients with weakened immune systems.

Fingolimod can cause vision problems and may increase the risk posterior reversible encephalopathy syndrome. Other serious risks include respiratory problems, liver injury, increased blood pressure, and skin cancer.

Fingolimod can cause harm to a developing fetus; women of child-bearing age should be advised of the

(*Gilenya—Novartis*)

FDA approves first drug to treat MS in pediatric patients

potential risk to the fetus and to use effective contraception.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/fda-approves-first-drug-treat-ms-pediatric-patients>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

May 14, 2018

Polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride, and potassium chloride for oral solution

(Plenvu—Valeant/Salix)

Lower-volume bowel cleansing prep for colonoscopies receives FDA approval

Uses/Notes

[Salix Pharmaceuticals announced](#) FDA approval of polyethylene glycol 3350, sodium ascorbate, sodium sulfate, ascorbic acid, sodium chloride, and potassium chloride for oral solution, a lower-volume (1L) polyethylene glycol based (PEG) bowel preparation, under the trade name Plenvu.

Plenvu is the lowest, total-volume preparation bowel cleanser available in the United States, according to Salix.

Approval was based on multiple Phase III clinical trials, including the NOCT study, which compared Plenvu versus a trisulfate bowel cleansing solution (Suprep) using a two-day split-dosing regimen in adults. Both primary endpoints were met, achieving noninferior overall bowel cleansing success and “excellent plus good” cleansing of the ascending colon.

Plenvu is also the only FDA-approved bowel cleanser to offer split dosing on the same day as the colonoscopy procedure.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/lower-volume-bowel-cleansing-prep-colonoscopies-receives-fda-approval>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

May 15, 2018

Epoetin alfa-epbx

(Retacrit—Hospira)

FDA approves first epoetin alfa biosimilar for treatment of anemia

Uses/Notes

FDA approved [epoetin alfa-epbx](#) as a biosimilar to epoetin alfa (Epogen/Procrit) to treat anemia caused by chronic kidney disease, chemotherapy, or use of zidovudine in patients with HIV infection.

Epoetin alfa-epbx is also approved for use before and after surgery to reduce the chance that red blood cell transfusions will be needed because of blood loss during surgery.

Approval 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 demonstrate the product is biosimilar to epoetin alfa. It has been approved as a [biosimilar](#), not as an [interchangeable product](#).

The most common adverse effects in clinical studies of the reference product were high blood pressure, joint pain, muscle spasm, fever, dizziness, medical device malfunction, blood vessel blockage, respiratory infection, cough, rash, injection site irritation, nausea, vomiting, muscle pain, inflammation of the mouth and lips, weight decrease, reduction in white blood cells, bone pain, high blood sugar, insomnia, headache, depression, difficulty swallowing, low blood potassium, blood clots, itching, headache, injection site pain, and chills.

Like epoetin alfa, the biosimilar must be dispensed with a patient Medication Guide and contains a boxed warning to alert health professionals and patients about increased risks of death, heart problems, stroke, and tumor growth or recurrence.

Additional warnings include high blood pressure; seizures; a condition in which the bone marrow stops making red blood cells, thus causing anemia; serious allergic reactions; and severe skin reactions.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/fda-approves-first-epoetin-alfa-biosimilar-treatment-anemia>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

May 17, 2018

Lucemyra

Uses/Notes

FDA has approved [lofexidine hydrochloride](#), an oral, selective alpha 2-adrenergic receptor agonist that reduces the release of norepinephrine, to mitigate withdrawal symptoms from abrupt discontinuation of opioids in adults.

Norepinephrine is believed to play a role in many of the symptoms of opioid withdrawal. While the agent may lessen the severity of withdrawal symptoms, it may not completely prevent them and is only approved for treatment for up to 14 days.

It is not a treatment for opioid use disorder (OUD) but can be used as part of a broader, long-term treatment plan for managing OUD.

In patients using opioid analgesics appropriately as prescribed, opioid withdrawal is typically managed by slow taper of the medication, which is intended to avoid or lessen the effects of withdrawal while allowing the body to adapt to not having the opioid.

In patients with OUD, withdrawal is typically managed by substitution of another opioid, followed by gradual reduction or transition to maintenance therapy with FDA-approved medication-assisted treatment drugs such as methadone, buprenorphine or naltrexone; or by various medications aimed at specific symptoms, such as OTC remedies for upset stomach or aches and pains. Other treatments may also be prescribed.

Safety and efficacy of lofexidine were supported by two randomized, double-blind, placebo-controlled clinical trials of 866 adults meeting Diagnostic and Statistical Manual–IV criteria for opioid dependence who were physically dependent on opioids and undergoing abrupt opioid discontinuation.

The studies evaluated benefit using the Short Opiate Withdrawal Scale of Gossop (SOWS-Gossop), a patient-reported outcome instrument that assesses opioid withdrawal symptoms such as stomach cramps, muscle spasms/twitching, feeling of coldness, heart pounding, muscular tension, aches and pains, yawning,

(Lofexidine hydrochloride—US WorldMeds)

FDA approves first nonopioid to mitigate opioid withdrawal symptoms

runny eyes, and insomnia or problems sleeping.

For each opioid withdrawal symptom, patients are asked to rate their symptom severity using four response options (none, mild, moderate, and severe), with the SOWS-Gossop total score ranging from 0 to 30. A higher score indicated a greater withdrawal symptom severity. SOWS-Gossop scores were lower for patients treated with lofexidine compared with placebo, and more patients completed the treatment period of the studies in the lofexidine group compared with the placebo group.

The most common adverse effects included hypotension, bradycardia, somnolence, sedation, and dizziness. Lofexidine was also associated with a few cases of fainting. It also affects the heart's electrical activity, which can increase the risk of abnormal heart rhythms. When the agent is stopped, patients can experience a marked increase in blood pressure.

Safety and efficacy have not been established in children or adolescents younger than 17 years of age. After a period of not using opioid drugs, patients may be more sensitive to the effects of lower amounts of opioids if relapse does occur, and taking opioids in amounts that were used before withdrawing from opioids can lead to overdose and death.

FDA is requiring 15 postmarketing studies, including both animal and human studies.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-first-nonopioid-mitigate-opioid-withdrawal-symptoms>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

May 18, 2018

Erenumab-aooe

(Aimovig—Amgen)

Novel once-monthly drug prevents migraines in adults

Uses/Notes

FDA has approved [erenumab-aooe](#) for once-monthly preventive treatment of migraine in adults.

Given by self-injection, it is the first FDA-approved preventive migraine treatment in a new class of drugs that work by blocking the activity of calcitonin gene-related peptide, a molecule involved in migraine attacks.

“Aimovig provides patients with a novel option for reducing the number of days with migraine,” said an FDA spokesperson.

Effectiveness of the agent to prevent migraine was evaluated in three clinical trials. The first study, which included 955 participants with a history of episodic migraine, compared erenumab-aooe with placebo. Over a 6-month period, patients treated with erenumab-aooe experienced, on average, one to two fewer monthly migraine days than those on placebo.

The second study included 577 patients with a history of episodic migraine and compared erenumab-aooe with placebo. Over 3 months, patients experienced, on average, one fewer migraine day per month than those on placebo.

In the third study of 667 patients with a history of chronic migraine, patients treated with erenumab-aooe over the course of 3 months experienced, on average, 2.5 fewer monthly migraine days than those receiving placebo.

The most common adverse effects were injection-site reactions and constipation.

Source URL:

<http://www.aphadruginfo.com/new-drug-approvals/novel-once-monthly-drug-prevents-migraines-adults>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

May 23, 2018

Avatrombopag

(Doptelet—AkaRx)

FDA approves new drug for patients with chronic liver disease

Uses/Notes

[FDA approved](#) avatrombopag tablets to treat low blood platelet count (thrombocytopenia) in adults with chronic liver disease who are scheduled to undergo a medical or dental procedure. This is the first drug approved by FDA for this use.

Thrombocytopenia is a condition in which there is a lower-than-normal number of circulating platelets in the blood. When patients have moderately to severely reduced platelet counts, serious or life-threatening bleeding can occur, especially during invasive procedures. Patients with significant thrombocytopenia typically receive platelet transfusions immediately prior to a procedure to increase the platelet count.

Safety and efficacy of avatrombopag were studied in two trials (ADAPT-1 and ADAPT-2) involving 435 patients with chronic liver disease and severe thrombocytopenia who were scheduled to undergo a procedure that would typically require platelet transfusion. The trials investigated two dose levels of avatrombopag administered orally over 5 days compared with placebo.

The trial results showed that for both dose levels of avatrombopag, a higher proportion of patients had increased platelet counts and did not require platelet transfusion or any rescue therapy on the day of the procedure and up to 7 days following the procedure, compared with those treated with placebo.

The most common adverse effects reported by clinical trial participants who received avatrombopag were fever, abdominal pain, nausea, headache, fatigue, and edema. People with chronic liver disease and people with certain blood clotting conditions may have an increased risk of developing blood clots when taking avatrombopag.

This product was granted Priority Review, under which the FDA's goal is to take action on an application within 6 months where the agency determines that the drug, if approved, would significantly improve the safety or effectiveness of treating, diagnosing, or preventing a serious condition.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-new-drug-patients-chronic-liver-disease>

Alerts and Recalls

Generic Name (Trade Name—Company)

May 23, 2018

Gadolinium-based contrast agents

(Multiple trade names—Multiple companies)

FDA warns GBCAs are retained in the body, requires new class warnings

Uses/Notes

FDA is requiring a [new class warning](#) and other safety measures for all gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI) concerning gadolinium remaining in patients' bodies, including the brain, for months to years after receiving these drugs.

Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and the agency has concluded that the benefit of all approved GBCAs continues to outweigh any potential risks.

However, after additional review and consultation with the [Medical Imaging Drugs Advisory Committee](#), FDA is requiring several actions to alert health professionals and patients about gadolinium retention after an MRI using a GBCA, and actions that can help minimize problems.

These include requiring a new patient Medication Guide that every patient will be asked to read before receiving a GBCA. FDA is also requiring manufacturers of GBCAs to conduct human and animal studies to further assess the safety of these contrast agents.

GBCAs are used with MRI scanners to examine the body for problems such as cancer, infections, or bleeding. GBCAs contain gadolinium, a heavy metal. After being administered, GBCAs are mostly eliminated from the body through the kidneys. However, trace amounts of gadolinium may stay in the body long-term. Many GBCAs have been on the market for more than a decade.

Health professionals should consider the retention characteristics of each agent when choosing a GBCA for patients who may be at higher risk for gadolinium retention. These patients include those requiring multiple lifetime doses, pregnant women, children, and patients with inflammatory conditions. Minimize repeated GBCA imaging studies when possible, particularly closely spaced MRI studies. However, do not avoid or defer necessary GBCA MRI scans.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/fda-warns-gbcas-are-retained-body-requires-new-class-warnings-0>

Alerts and Recalls

Generic Name (Trade Name—Company)

May 23, 2018

Dolutegravir

(Tivicay—ViiV Healthcare)

FDA evaluating potential risk of neural tube birth defects with HIV med

Uses/Notes

[FDA is alerting](#) the public that serious cases of neural tube birth defects involving the brain, spine, and spinal cord have been reported in babies born to women who took dolutegravir for HIV treatment.

Preliminary results from an ongoing observational study in Botswana found that women who received dolutegravir at the time of becoming pregnant or early in the first trimester appear to be at higher risk for these defects.

Dolutegravir is an FDA-approved antiretroviral medicine used in combination with other antiretroviral medicines to treat HIV/AIDS. Dolutegravir works by blocking integrase, an HIV enzyme, to prevent the virus from multiplying and can reduce the amount of HIV in the body.

Approved in 2013, dolutegravir has been on the market for 5 years, and is available as a single ingredient product under the brand name Tivicay and as a fixed-dose combination tablet with other HIV medicines under the brand names Juluca and Triumeq.

Ongoing monitoring will continue as part of the observational study in Botswana. Additional birth outcomes are projected from pregnant women who were exposed to dolutegravir at the time of becoming pregnant.

To date, this observational study has found no reported cases of babies born with neural tube defects to women starting dolutegravir later in pregnancy. FDA is investigating this new safety issue and will update the public when it has more information.

To monitor birth outcomes of pregnant women, report pregnancy exposures to the Antiretroviral Pregnancy Registry at 800-258-4263.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/fda-evaluating-potential-risk-neural-tube-birth-defects-hiv-med>

Alerts and Recalls

Generic Name (Trade Name—Company)

May 23, 2018

Pembrolizumab, atezolizumab

Uses/Notes

[FDA is alerting](#) health professionals, oncology clinical investigators, and the public about decreased survival associated with use of pembrolizumab or atezolizumab in clinical trials treating 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).

In two ongoing clinical trials (KEYNOTE-361 and IMVIGOR-130), patients with PD-L1 low status in the monotherapy arms had decreased survival compared with patients who received cisplatin- or carboplatin-based chemotherapy. There was no change in the adverse event profile of pembrolizumab or atezolizumab.

Both Merck, manufacturer of pembrolizumab, and Genentech, manufacturer of atezolizumab, have stopped enrolling patients whose tumors have PD-L1 low status to the pembrolizumab or atezolizumab monotherapy arms.

Both agents are currently approved for treatment of locally advanced or metastatic urothelial carcinoma patients who are not eligible for cisplatin-containing chemotherapy, irrespective of PD-L1 status.

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

Health professionals should be aware that the populations enrolled in the ongoing clinical trials were eligible for platinum-containing chemotherapy and therefore differ from those enrolled in the trials that led to the accelerated approvals of both pembrolizumab or atezolizumab for treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

FDA recommends providers select patients for treatment of locally advanced or metastatic urothelial cancer using the criteria described in Section 14 of each label. These criteria supported the approvals for pembrolizumab and

(Keytruda, Tecentriq—Merck, Genentech)

Decreased survival associated with agents used as monotherapy in two ongoing clinical trials

atezolizumab for initial monotherapy in cisplatin-ineligible patients.

The agents are also currently FDA approved for treatment of multiple types of other cancers.

Source URL:

<http://www.aphadruonline.com/alerts-and-recalls/decreased-survival-associated-agents-used-monotherapy-two-ongoing-clinical-trials>

Alerts and Recalls

Generic Name (Trade Name—Company)

May 23, 2018

Benzocaine

Uses/Notes

[FDA is warning](#) that OTC teething products containing the pain reliever benzocaine pose a serious risk of methemoglobinemia in infants and children younger than 2 years old and should no longer be used, marketed, or sold.

This dangerous condition is the result of elevated levels of methemoglobin in the blood and can lead to death. It causes the amount of oxygen carried through the blood to be greatly reduced.

Benzocaine is marketed to help relieve pain from a variety of conditions such as teething, sore throat, canker sores, and irritation of the mouth and gums. The products are sold as gels, sprays, ointments, solutions, and lozenges under the OTC brand names Anbesol, Baby Orajel, Cepacol, Chloraseptic, Hurrricane, Orabase, Orajel and Topex, as well as store brands and generics.

Signs and symptoms of methemoglobinemia include pale or gray- or blue-colored skin, lips, and nail beds; shortness of breath; fatigue; headache; lightheadedness; and rapid heart rate. These adverse effects may occur after using benzocaine for the first time or after prior uses and may appear within minutes to 1 to 2 hours after using benzocaine. If any of these symptoms occur, the person should receive medical attention immediately.

FDA is requiring manufacturers of all FDA-approved prescription local anesthetics to standardize warning information about the risk of methemoglobinemia in product labeling across this class of products. Manufacturers of approved, prescription local anesthetics will have 30 days to reply to FDA's letter about these new safety labeling changes. If companies do not comply, FDA stated it will initiate a regulatory action to remove these products from the market. Also, the agency is requesting that companies add new warnings to all other benzocaine oral health products to describe certain serious risks.

FDA also previously cautioned parents and caregivers

(Multiple trade names—Multiple companies) to [not give certain homeopathic teething tablets](#) to children and to seek advice from their health professional for safe alternatives.

OTC teething products containing benzocaine pose serious risk to infants, children

When buying OTC oral health drug products, consumers should refer to the [OTC Drug Facts Label](#) to see if benzocaine is an active ingredient.

For advice on treating teething pain, FDA suggests the [American Academy of Pediatrics' \(AAP\) recommendations](#).

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/otc-teething-products-containing-benzocaine-pose-serious-risk-infants-children>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

May 23, 2018

Fluticasone furoate

(*Arnuity Ellipta*—*GlaxoSmithKline*)

Once-daily inhaled corticosteroid approved to treat asthma in children aged 5 to 11 years

Uses/Notes

GlaxoSmithKline [announced](#) FDA approval of fluticasone furoate, a once-daily inhaled corticosteroid, for maintenance treatment of asthma in children aged 5 to 11 years.

The drug is delivered as a 50-mcg, once-daily dose using the Ellipta inhaler. It is not indicated for relief of acute bronchospasm.

The product was approved in August 2014 for maintenance treatment of asthma in patients aged 12 years and older.

Approval was based on data from a pivotal study assessing the efficacy and safety of once-daily fluticasone furoate, compared with placebo, in 593 children aged 5 to 11 years (inclusive) with asthma. Inhaled fluticasone propionate 100 mcg twice daily was included as an active control.

Results showed statistically significant improvements with once-daily fluticasone furoate 50 mg compared with placebo (19.5 L/min; $P < .001$).

The most common adverse reactions, reported in 73% of pediatric subjects aged 5 to 11 years, are pharyngitis, bronchitis, and viral infection.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/once-daily-inhaled-corticosteroid-approved-treat-asthma-children-aged-5-11>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

May 23, 2018

Sodium zirconium cyclosilicate

(Lokelma—AstraZeneca)

New agent provides rapid and sustained potassium control in adults with hyperkalaemia

Uses/Notes

AstraZeneca announced FDA approval of [sodium zirconium cyclosilicate](#), a highly selective, oral potassium-removing agent, to treat adults with hyperkalaemia. The agent is formulated as a powder for oral suspension and administered orally.

Hyperkalaemia occurs in 23% to 47% of patients with chronic kidney disease and/or heart failure, with an estimated 200 million and 38 million people, respectively, living with each condition worldwide. The condition may lead to cardiac arrest and death, with mortality being up to 30% in patients with severe hyperkalaemia, if not treated rapidly.

The risk of hyperkalaemia increases significantly for patients with chronic kidney disease and for those who take common medications for heart failure, such as renin-angiotensin-aldosterone system (RAAS) inhibitors, which can increase potassium in the blood. To help prevent the recurrence of hyperkalaemia, RAAS-inhibitor therapy is often modified or discontinued, which can compromise cardio-renal outcomes and increase the risk of death.

FDA approval was supported by data from three double-blind, placebo-controlled trials and two open-label trials. For patients receiving sodium zirconium cyclosilicate, the onset of action was at 1.0 hour, and the median time to achieving normal potassium levels in the blood was 2.2 hours, with 92% of patients achieving normal potassium levels within 48 hours from baseline. The treatment effect was maintained for up to 12 months.

Source URL:

<http://www.aphadruginfo.com/new-drug-approvals/new-agent-provides-rapid-and-sustained-potassium-control-adults-hyperkalaemia>

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