
A^{PhA} **DrugInfoLine[®]**

November 2018

Cardiology

Advising on this article: Eric MacLaughlin

November 5, 2018

A bleak picture of aspirin for primary prevention in older adults

Key Point

Three publications in the New England Journal of Medicine from the ASPREE trial showed that daily use of low-dose aspirin in healthy, community-dwelling older people without documented cardiovascular (CV) disease, dementia, or physical disability did not prolong disability-free survival, did not reduce the risk of CV disease (CVD), and was associated with a higher risk of all-cause mortality and major hemorrhage compared with placebo.

Source URL:

<http://www.aphadruginfoline.com/cardiology/bleak-picture-aspirin-primary-prevention-older-adults>

[Respiratory](#)

Advising on this article: Roy A. Pleasants, II

November 5, 2018

A personalized approach to COPD management is needed

Key Point

A small decline in lung function with no change in the rate of exacerbations was observed in patients with infrequent exacerbations and moderate to severe chronic obstructive pulmonary disease (COPD) who had been on long-term triple therapy and were subsequently de-escalated to dual therapy, according to data published in the American Journal of Respiratory and Critical Care Medicine.

Source URL:

<http://www.aphadruginfoline.com/respiratory/personalized-approach-copd-management-needed>

[OTC Medicines Corner](#)

Advising on this article: Tara Whetsel

November 13, 2018

Folic acid and multivitamin use may decrease autism risk

Key Point

Maternal exposure to folic acid and/or multivitamins (MVI) before and during pregnancy was associated with a lower risk of autism spectrum disorder in the child compared with no exposure, according to results of a case-control study published in JAMA Psychiatry.

Source URL:

<http://www.aphadruonline.com/otc-medicines-corner/folic-acid-and-multivitamin-use-may-decrease-autism-risk>

[Focus on Immunizations](#)

Advising on this article: John D. Grabenstein

November 13, 2018

Adolescent vaccinations not associated with fertility problems

Key Point

Adolescent vaccinations with HPV, Tdap, inactivated influenza, and meningococcal conjugate (MenACWY) were not associated with an increased risk of primary ovarian insufficiency, according to results of a retrospective cohort study published in Pediatrics.

Source URL:

<http://www.aphadruginfoline.com/focus-immunizations/adolescent-vaccinations-not-associated-fertility-problems>

[Neurology](#)

Advising on this article: Jack J. Chen

November 20, 2018

Pharmacists need a better understanding of generic drug approvals

Key Point

An assessment of community pharmacists' understanding of FDA therapeutic equivalence standards and bioequivalence criteria showed that many pharmacists need additional education on these topics, according to survey results published in *Research in Social and Administrative Pharmacy*.

Source URL:

<http://www.aphadruonline.com/neurology/pharmacists-need-better-understanding-generic-drug-approvals>

[Focus on Lipids Care](#)

Advising on this article: Amber L. Briggs

November 20, 2018

Reassessing use of statins for primary prevention in older adults

Key Point

In people older than age 74 years without diabetes, statin use for primary prevention was not associated with a reduction in the risk of atherosclerotic cardiovascular (CV) disease or all-cause mortality, with benefits seen only in those with diabetes who were between 75 and 84 years old, according to results of an observational study published in BMJ.

Source URL:

<http://www.aphadruginfoline.com/focus-lipids-care/reassessing-use-statins-primary-prevention-older-adults>

[OTC Medicines Corner](#)

Advising on this article: Tara Whetsel

November 27, 2018

Factors that may predict sustained efficacy after a short course of OTC PPIs

Key Point

Heartburn resolution within 7 days following completion of a 2-week course of OTC proton pump inhibitor (PPI) therapy (i.e., esomeprazole) was more common in patients who had less baseline heartburn frequency, in those who had symptom resolution during the last 7 days of treatment, and in patients who had the most heartburn-free days during the 2-week treatment period, according to results of a post-hoc analysis published in BMC Gastroenterology.

Source URL:

<http://www.aphadruginfoline.com/otc-medicines-corner/factors-may-predict-sustained-efficacy-after-short-course-otc-pis>

[Psychiatry](#)

Advising on this article:

November 27, 2018

Medications used for substance abuse disorders may reduce suicidality, crime

Key Point

Use of medications for alcohol or opioid abuse (e.g., naltrexone, buprenorphine, methadone) was associated with reductions in accidental overdoses, suicidal behaviors, and crime, according to results of an observational, population-based study published in the American Journal of Psychiatry.

Source URL:

<http://www.aphadruginfoline.com/psychiatry/medications-used-substance-abuse-disorders-may-reduce-suicidality-crime>

Supplemental Approvals

Generic Name (Trade Name—Company)

November 1, 2018

Pembrolizumab

(Keytruda—Merck)

In combination with chemotherapy, drug approved for first-line treatment of metastatic squamous NSCLC

Uses/Notes

[FDA approved](#) a new indication for pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel as first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC).

Approval was based on a randomized, multicenter, double-blind, placebo-controlled trial in 559 patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease.

Patients were randomized (1:1) to pembrolizumab 200 mg or placebo in combination with carboplatin, along with either paclitaxel every 3 weeks or nab-paclitaxel weekly on a 3-week cycle for four cycles, followed by pembrolizumab or placebo. Patients continued pembrolizumab or placebo until disease progression, unacceptable toxicity, or a maximum of 24 months.

The trial demonstrated statistically significant improvements in patients receiving pembrolizumab plus chemotherapy compared with those randomized to placebo plus chemotherapy.

The most common adverse reactions in at least 20% of patients who received pembrolizumab were fatigue/asthenia, nausea, constipation, diarrhea, vomiting, pyrexia, decreased appetite, rash, cough, dyspnea, alopecia, and peripheral neuropathy.

The recommended pembrolizumab dose for metastatic squamous NSCLC is 200 mg intravenously every 3 weeks, prior to chemotherapy when given on the same day, until disease progression, unacceptable toxicity, or 24 months after initiation.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/combination-chemotherapy-drug-approved-first-line-treatment-metastatic>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

November 1, 2018

Adalimumab-adaz

(Hyrimoz—Sandoz)

Sandoz receives FDA approval for adalimumab biosimilar

Uses/Notes

[Sandoz announced](#) FDA approval of adalimumab-adaz (Hyrimoz), a biosimilar to adalimumab (Humira), for treatment of rheumatoid arthritis, juvenile idiopathic arthritis in patients aged 4 years and older, psoriatic arthritis, ankylosing spondylitis, adult Crohn's disease, ulcerative colitis, and plaque psoriasis.

The drug, a tumor necrosis factor inhibitor administered subcutaneously by injection, is the third FDA-approved biosimilar to adalimumab.

Approval was based on a randomized, double-blind, three-arm, parallel biosimilarity study that confirmed the pharmacokinetics, immunogenicity, and safety of adalimumab-adaz. The study met the primary endpoint, demonstrating bioequivalence for all primary pharmacokinetic parameters.

A confirmatory efficacy and safety biosimilarity study demonstrated therapeutic equivalence in the sensitive indication of patients with moderate to severe chronic plaque-type psoriasis, with a similar safety and immunogenicity profile to the reference biologic.

The most common adverse reactions (incidence > 10%) were infections (e.g., upper respiratory, sinusitis), injection-site reactions, headache, and rash.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/sandoz-receives-fda-approval-adalimumab-biosimilar>

Alerts and Recalls

Generic Name (Trade Name—Company)

November 1, 2018

Irbesartan

Uses/Notes

[FDA is alerting](#) patients and health professionals to ScieGen's voluntary [recall](#) of certain lots of irbesartan, an angiotensin II receptor blocker (ARB), because they contain *N*-nitrosodiethylamine (NDEA), a known animal and suspected human carcinogen.

FDA laboratory testing confirmed NDEA in some lots of ScieGen's irbesartan. ScieGen's irbesartan products are labeled as Westminster Pharmaceuticals and Golden State Medical Supply (GSMS). See the [list of irbesartan products under recall](#).

This is the first nonvalsartan drug product the agency has found to contain the NDEA impurity.

In addition, Aurobindo, which manufactures the active pharmaceutical ingredient (API) for ScieGen's irbesartan products, is [recalling](#) all unexpired lots of its irbesartan API supplied to the U.S. market with NDEA. FDA and Aurobindo laboratory testing confirmed NDEA in certain lots of the Aurobindo's irbesartan API.

FDA reminds patients taking any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. Not all ARBs contain NDEA or *N*-nitrosodimethylamine (NDMA), so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

To date, ScieGen is the only manufacturer of irbesartan drug products found to contain NDEA.

FDA continues to test all ARBs for the presence of impurities and has publicly posted two methods for manufacturers and regulatory agencies around the world to test their ARBs for the unexpected NDMA and NDEA impurities. The [combined headspace method](#) and the [combined direct injection method](#) can detect and quantify NDMA and NDEA simultaneously in ARB API and finished drug products.

FDA continues to work with API and drug manufacturers

(No trade names—*ScieGen*)

Some lots of irbesartan recalled because they contain NDEA carcinogen

to ensure their products are not at risk for NDMA or NDEA formation.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/some-lots-irbesartan-recalled-because-they-contain-ndea-carcinogen>

[Alerts and Recalls](#)

Generic Name (Trade Name—Company)

November 1, 2018

Irbesartan

(No trade names—Aurobindo)

Aurobindo recalls 22 batches of drug substance because of NDEA impurity

Uses/Notes

[Aurobindo Pharma is voluntarily recalling](#) 22 batches of irbesartan drug substance because they contain *N*-nitrosodiethylamine (NDEA). NDEA, which occurs naturally in certain foods, drinking water, air pollution, and industrial processes, has been classified as a probable human carcinogen by the International Agency for Research on Cancer.

These 22 batches of irbesartan drug substance were supplied to ScieGen Pharmaceuticals to manufacture the finished irbesartan drug product.

Aurobindo has notified ScieGen of the recall and is arranging for the return of all available irbesartan drug substance. Aurobindo Pharma Limited has further advised ScieGen to contact its distributors and retailers to return irbesartan drug product and finished irbesartan tablets that have been identified by Aurobindo.

Patients should contact their pharmacist or physician for advise on an alternative treatment before returning their medication. Patients who are on irbesartan should continue taking their medication, as the risk of harm to a patient's health may be higher if treatment is stopped immediately without an alternative treatment.

Source URL:

<http://www.aphaduginfoline.com/alerts-and-recalls/aurobindo-recalls-22-batches-drug-substance-because-ndea-impurity>

Alerts and Recalls

Generic Name (Trade Name—Company)

November 13, 2018

Epinephrine auto-injectors

(EpiPen, Epi-Pen Jr.—Mylan)

Some EpiPen auto-injectors may not readily slide out of carrier tube

Uses/Notes

FDA is alerting patients, caregivers, and health professionals that the labels attached to some EpiPen 0.3 mg and EpiPen Jr 0.15 mg auto-injectors, and the authorized generic versions, may block access to the auto-injector and prevent the ability to easily access the product.

In a [letter](#) to health professionals from Pfizer, the manufacturer of the Mylan EpiPen, the label sticker on the auto-injector unit may have been improperly applied, causing resistance when removing it from the carrier tube. The carrier tube is the immediate package in which the auto-injector is contained. In some cases, the patient or caregiver may not be able to quickly remove the epinephrine auto-injector from the carrier tube.

The auto-injector device and the epinephrine it delivers are not affected by this issue and can be used as prescribed. It is vital for lifesaving products to work as designed in an emergency situation, and patients and caregivers should inspect their epinephrine auto-injector prior to needing it to ensure they can quickly access the product.

The letter also describes how to inspect potentially affected products and explains that patients should contact Mylan Customer Relations at 800-796-9526 if an auto-injector does not slide out easily from the carrier tube OR the label is not fully adhered to the auto-injector. Pharmacists should inspect the products before dispensing them to patients to ensure quick access to the auto-injector and should not dispense any product that does not slide easily out of its carrier tube.

FDA is not aware of any adverse event reports associated with improperly applied EpiPen or EpiPen Jr auto-injectors, or their authorized generics label. As stated on the product label, consumers should always seek emergency medical help right away after using their epinephrine auto-injector.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/some-epipen-auto-injectors-may-not-readily-slide-out-carrier-tube>

Supplemental Approvals

Generic Name (Trade Name—Company)

November 13, 2018

Lorlatinib

(Lorbrena—Pfizer)

**Lorlatinib approved for previously treated
ALK-positive metastatic NSCLC**

Uses/Notes

[Pfizer announced](#) FDA approval of a new indication for lorlatinib, a third-generation anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) for patients with ALK-positive metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on crizotinib and at least one other ALK inhibitor for metastatic disease; or whose disease has progressed on alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease.

Accelerated approval was based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

While many ALK-positive metastatic NSCLC patients respond to initial TKI therapy, they typically experience tumor progression, stated Pfizer in a news release. In addition, options for patients who progress after treatment with second-generation ALK TKIs, alectinib, brigatinib and ceritinib, are limited. Approval of this indication represents a new option for patients who have progressed on a second-generation ALK TKI, providing an opportunity to remain on oral therapy.

In clinical trials, the most common (~20%) adverse reactions were edema, peripheral neuropathy, cognitive effects, dyspnea, fatigue, weight gain, arthralgia, mood effects, and diarrhea.
increased alkaline phosphatase.

The most frequent serious adverse reactions reported were pneumonia, dyspnea, pyrexia, mental status changes, and respiratory failure.

Fatal adverse reactions occurred in 2.7% percent of patients and included pneumonia, myocardial infarction, acute pulmonary edema, embolism, peripheral artery occlusion, and respiratory distress.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/lorlatinib-approved-previously-treated-alk-positive-metastatic-nsclc>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

November 13, 2018

Revefenacin inhalation solution

(Yupelri—Theravance BioPharma, Mylan)

New drug approved for maintenance treatment of adults with COPD

Uses/Notes

FDA approved [revefenacin inhalation solution](#) for maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). Revefenacin is a long-acting muscarinic antagonist, a class of medicines that improve lung function in patients with COPD. The agent is administered once daily via a standard jet nebulizer.

As with other inhaled medicines, revefenacin can cause paradoxical bronchospasm (wheezing). If paradoxical bronchospasm occurs, patients should discontinue use. Patients should also be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual changes). Patients should consult a health professional immediately if any of these signs or symptoms develop.

The most common adverse reactions include cough, nasopharyngitis, upper respiratory tract infection, headache, and back pain. Health professionals should avoid administering revefenacin with other anticholinergic-containing drugs. The agency does not recommend administering revefenacin at the same time as OATP1B1 and OATP1B3 inhibitors (e.g. rifampicin, cyclosporine, etc.), as it may lead to an increase in exposure of the active metabolite.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/new-drug-approved-maintenance-treatment-adults-copd>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

November 26, 2018

Glasdegib

Uses/Notes

FDA has [approved](#) glasdegib tablets to be used in combination with low-dose cytarabine (LDAC), a type of chemotherapy, for the treatment of newly diagnosed acute myeloid leukemia (AML) in adults aged 75 or older or who have other chronic health conditions or diseases that may preclude the use of intensive chemotherapy.

Efficacy of glasdegib was studied in a randomized clinical trial in which 111 adult patients with newly diagnosed AML were treated with either glasdegib in combination with LDAC or LDAC alone. The trial measured overall survival (OS) from the date of randomization to death from any cause. Results demonstrated a significant improvement in OS in patients treated with glasdegib. The median OS was 8.3 months for patients treated with glasdegib plus LDAC compared with 4.3 months for patients treated with LDAC only.

Common adverse effects in clinical trials were anemia, fatigue, hemorrhage, febrile neutropenia, muscle pain, nausea, edema, low platelet counts, shortness of breath, decreased appetite, distorted taste, pain or sores in the mouth or throat, constipation and rash.

The prescribing information includes a boxed warning about the risk of embryo-fetal death or severe birth defects. Glasdegib should not be used during pregnancy or while breastfeeding. Pregnancy testing should be conducted in females of reproductive age before treatment initiation, and effective contraception should be used during treatment and for at least 30 days after the last dose.

The boxed warning also advises male patients of the potential risk of drug exposure through semen and to use condoms with a pregnant partner or a female partner who could become pregnant both during treatment and for at least 30 days after the last dose.

Glasdegib must be dispensed with a patient Medication Guide that describes important information about the drug's uses and risks. Patients should also be advised not to donate blood or blood products during treatment.

(Daurismo—Pfizer)

FDA approves new treatment for acute myeloid leukemia

Health care providers should also monitor patients for QT prolongation.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-new-treatment-acute-myeloid-leukemia>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

November 26, 2018

Emapalumab-lzsg

(*Gamifant—Novimmune SA*)

FDA approves first treatment for patients with rare and life-threatening immune disease

Uses/Notes

FDA approved [emapalumab-lzsg](#) for the treatment of pediatric (newborn and above) and adult patients with primary hemophagocytic lymphohistiocytosis (HLH) who have refractory, recurrent, or progressive disease or intolerance to conventional HLH therapy. This FDA approval is the first for a drug specifically for HLH.

HLH is a condition in which the body's immune cells do not work properly and start to damage the body's own organs, including the liver, brain, and bone marrow. It can be inherited, which is known as primary or "familial" HLH. It can also have noninherited causes. People with primary HLH usually develop symptoms within the first months or years of life. Symptoms may include fever, enlarged liver or spleen, and decreased number of blood cells.

Emapalumab-lzsg efficacy was studied in a clinical trial of 27 pediatric patients with suspected or confirmed primary HLH with either refractory, recurrent, or progressive disease during conventional HLH therapy or who were intolerant of conventional HLH therapy. The median age of the patients in the trial was 1 year old.

The study showed that 63% of patients experienced a response, and 70% were able to proceed to stem cell transplant.

Common adverse effects in clinical trials included infections, hypertension, infusion-related reactions, low potassium, and fever.

Patients receiving the agent should not receive any live vaccines and should be tested for latent tuberculosis. Patients should be closely monitored and treated promptly for infections while receiving emapalumab-lzsg.

Source URL:

<http://www.aphadruginfo.com/new-drug-approvals/fda-approves-first-treatment-patients-rare-and-life-threatening-immune-disease>

Alerts and Recalls

Generic Name (Trade Name—Company)

November 26, 2018

Multiple generic names

(Multiple trade names—Pharm D Solutions)

FDA warns health professionals, patients not to use Pharm D Solutions' sterile drug products

Uses/Notes

FDA is [alerting](#) health professionals and patients not to use drug products intended to be sterile that are produced and distributed by Pharm D Solutions in Houston, TX, because they lack sterility assurance. Administration of a nonsterile drug product intended to be sterile may result in serious and potentially life-threatening infections or death.

Health professionals should immediately check their medical supplies, quarantine any purportedly sterile drug products, and not administer them to patients. They should also make alternative arrangements to obtain any medications they administer to patients from reliable sources that adhere to proper quality standards.

FDA issued a [warning letter](#) to Pharm D Solutions in December 2016 following an inspection. During FDA's recent follow-up inspection of Pharm D's compounding facility in August 2018, investigators observed insanitary conditions, including poor sterile production practices and deficient environmental monitoring. These conditions raised concerns about the company's ability to ensure the sterility of its drug products.

On September 10, 2018, following FDA's recommendation, Pharm D recalled all unexpired drug products intended to be sterile and agreed to cease sterile operations until it makes adequate corrections at its facility. However, Pharm D resumed sterile operations on October 8, 2018, and distributed purportedly sterile products without making adequate corrections at the facility. Pharm D agreed to cease sterile operations again on November 9, 2018, but has not agreed to FDA's recommendation to recall all unexpired drug products intended to be sterile. These compounded drug products could put patients at risk.

Pharm D is registered as an [outsourcing facility](#) under section 503B of the Federal Food, Drug, and Cosmetic Act. The Drug Quality and Security Act, signed into law on Nov. 27, 2013, added a new section 503B to the FD&C Act. Under section 503B, a compounder can elect to register as an outsourcing facility.

Source URL:

<http://www.aphadruinfo.com/alerts-and-recalls/fda-warns-health-professionals-patients-not-use-pharm-d-solutions-sterile-drug>

[Alerts and Recalls](#)

Generic Name (Trade Name—Company)

November 26, 2018

Fingolimod

Uses/Notes

[FDA is warning](#) that when the multiple sclerosis (MS) medicine fingolimod is stopped, the disease can become much worse than before the medicine was started or while it was being taken. This MS worsening is rare but can result in permanent disability.

As a result, the agency has added a new warning about this risk to the prescribing information of the fingolimod [drug label](#) and patient [Medication Guide](#).

Fingolimod, approved in the United States in 2010, is one of several medicines approved to treat relapsing MS.

Health professionals should inform patients before starting treatment about the potential risk of severe increase in disability after stopping the medication. When fingolimod is stopped, patients should be carefully observed for evidence of an exacerbation of their MS and treated appropriately.

Patients should be advised to seek immediate medical attention if they experience new or worsened symptoms of MS after fingolimod is stopped. These symptoms vary and include new or worsened weakness, increased trouble using arms or legs, or changes in thinking, eyesight, or balance. Treatment may have to be stopped for reasons such as adverse drug reactions, planned or unplanned pregnancy, or because the medicine is not working. However, patients should not stop taking it without first talking to their prescribers.

In the 8 years since fingolimod was approved in September 2010, FDA identified 35 cases of severely increased disability accompanied by the presence of multiple new lesions on magnetic resonance imaging that occurred 2 to 24 weeks after fingolimod was stopped. Most patients experienced this worsening in the first 12 weeks after stopping. FDA's analyses included only reports submitted to FDA and those found in the medical literature, so the agency said there may be additional cases about which it is unaware.

The severe increase in disability in these patients was

(Gilenya—Novartis)

Severe worsening of MS symptoms may occur after stopping fingolimod

more severe than typical MS relapses, and in cases where baseline disability was known, appeared unrelated to the patients' prior disease state. Several patients who were able to walk without assistance prior to discontinuing fingolimod progressed to needing wheelchairs or becoming totally bedbound.

In patients experiencing worsening of disability after stopping fingolimod, recovery varied. Seventeen patients had partial recovery, 8 experienced permanent disability or no recovery, and 6 eventually returned to the level of disability they had before or during fingolimod treatment.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/severe-worsening-ms-symptoms-may-occur-after-stopping-fingolimod>

Alerts and Recalls

Generic Name (Trade Name—Company)

November 26, 2018

Multiple generic names

(Multiple trade names—Mylan)

Mylan recalls valsartan products found to contain NDEA

Uses/Notes

FDA is [alerting](#) patients and health professionals to Mylan's voluntary [recall](#) of 15 lots of valsartan-containing products that contain *N*-nitrosodiethylamine (NDEA).

Not all Mylan valsartan-containing products distributed in the United States are being recalled. Mylan is recalling only those lots of valsartan-containing products that tested positive for NDEA above the acceptable level. The agency continues to investigate and test all angiotensin II receptor blockers (ARBs) for the presence of NDEA and *N*-nitrosodimethylamine (NDMA) and is taking swift action when it identifies these impurities that are above acceptable levels.

FDA has updated lists of [valsartan products under recall](#) and [valsartan products not under recall](#).

In addition, FDA reminds patients taking this medication or any recalled ARB to continue taking their current medicine until their pharmacist provides a replacement or their doctor provides an alternative treatment option. It also is important to know not all ARBs contain NDMA or NDEA, so pharmacists may be able to provide a refill of medication not affected by the recall, or doctors may prescribe a different medication that treats the same condition.

FDA has also posted [questions and answers](#) to assist health professionals and patients.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/mylan-recalls-valsartan-products-found-contain-ndea>

Alerts and Recalls

Generic Name (Trade Name—Company)

November 26, 2018

Sodium chloride injection 0.9%

(No trade names—Fresenius Kabi USA)

Product recalled because stoppers for vials contain natural rubber latex

Uses/Notes

Fresenius Kabi USA is voluntarily [recalling](#) 163 lots of sodium chloride injection 0.9%, 10 mL fill in a 10-mL vial; and sodium chloride injection 0.9%, 20 mL fill in a 20-mL vial. The product is being recalled because the stoppers contain natural rubber latex.

The product insert states that stoppers for both the 10-mL and the 20-mL vials do not contain natural rubber latex; the tray label for the two vial sizes and the vial label for the 20-mL vial also state that the stoppers do not contain latex.

For the population most at risk, those with a severe allergic reaction to latex, there is probability of an anaphylactic reaction that could result in hospitalization or death.

To date, Fresenius Kabi USA has not received any reports of adverse events related to this recall.

See the [tables](#) for a full list of the affected lots, including lot numbers and expiration dates.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/product-recalled-because-stoppers-vials-contain-natural-rubber-late>
x

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

November 27, 2018

Larotrectinib

Uses/Notes

FDA granted accelerated [approval](#) to larotrectinib, a treatment for adult and pediatric patients whose cancers have a specific genetic biomarker.

This is the second time the agency has approved a cancer treatment based on a common biomarker across different types of tumors rather than the location in the body where the tumor originated. The approval marks a new paradigm in the development of cancer drugs that are “tissue agnostic,” said FDA in a news release. It follows the policies that the FDA developed in a [guidance document](#) released earlier this year.

Larotrectinib is indicated for the treatment of adult and pediatric patients with solid tumors that have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment.

Research has shown that the NTRK genes, which encode for TRK proteins, can become fused to other genes abnormally, resulting in growth signals that support the growth of tumors. NTRK fusions are rare but occur in cancers arising in many sites of the body. Prior to today’s approval, there had been no treatment for cancers that frequently express this mutation, like mammary analogue secretory carcinoma, cellular or mixed congenital mesoblastic nephroma, and infantile fibrosarcoma.

Efficacy of larotrectinib was studied in three clinical trials that included 55 pediatric and adult patients with solid tumors that had an identified NTRK gene fusion without a resistance mutation and were metastatic or where surgical resection was likely to result in severe morbidity. These patients had no satisfactory alternative treatments or had cancer that progressed following treatment.

Larotrectinib demonstrated a 75% overall response rate across different types of solid tumors. These responses were durable, with 73% of responses lasting at least 6

(Vitrakvi—Loxo Oncology)

New oncology drug targets specific genetic biomarker instead of tumor type

months, and 39% lasting 1 year or more at the time results were analyzed. Examples of tumor types with an NTRK fusion that responded to larotrectinib include soft tissue sarcoma, salivary gland cancer, infantile fibrosarcoma, thyroid cancer, and lung cancer.

Larotrectinib received an [accelerated approval](#), which enables FDA to approve drugs for serious conditions to fill an unmet medical need using clinical trial data that is thought to predict a clinical benefit to patients. Further clinical trials are required to confirm the agent's clinical benefit. The sponsor is conducting or plans to conduct these studies.

Common adverse effects in clinical trials included fatigue, nausea, cough, constipation, diarrhea, dizziness, vomiting, and increased AST and ALT enzyme blood levels in the liver. Health care providers are advised to monitor patient ALT and AST liver tests every 2 weeks during the first month of treatment, then monthly and as clinically indicated. Women who are pregnant or breastfeeding should not take larotrectinib because it may cause harm to a developing fetus or newborn baby. Patients should report signs of neurologic reactions such as dizziness.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/new-oncology-drug-targets-specific-genetic-biomarker-instead-tumor-type>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

November 27, 2018

Eltrombopag

(Promacta—Novartis)

Combined with standard immunosuppressive therapy, drug targets treatment-resistant SAA

Uses/Notes

[Novartis announced](#) that FDA has expanded the approval of eltrombopag for first-line treatment of adults and pediatric patients aged 2 years and older with severe aplastic anemia (SAA) when the drug is taken in combination with standard immunosuppressive therapy.

SAA is a rare, life-threatening, acquired blood disorder in which a patient's bone marrow fails to produce enough red blood cells, white blood cells, and platelets. As a result, people living with this serious disease may experience debilitating symptoms and complications, such as fatigue, trouble breathing, recurring infections, and abnormal bruising or bleeding that can limit their daily activities.

Eltrombopag is an oral thrombopoietin receptor agonist that is already approved for SAA in patients who have had an insufficient response to IST. It is also approved for adults and children with chronic immune thrombocytopenia (ITP) who are refractory to other treatments, and for the treatment of thrombocytopenia in patients with chronic hepatitis C virus (HCV) infection.

In the clinical study upon which approval was based, the most common adverse reactions reported (incidence ?5%) were abnormal liver function tests, rash, and skin discoloration, including hyperpigmentation.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/combined-standard-immunosuppressive-therapy-drug-targets-treatment-resistant>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

November 29, 2018

Pegfilgrastim-cbqv

(Udenyca—Coherus Biosciences)

FDA approves pegfilgrastim biosimilar

Uses/Notes

On November 2, Coherus BioSciences [announced](#) FDA approval of pegfilgrastim-cbqv, the first biosimilar of pegfilgrastim (Neulasta) approved by both FDA and the European Commission (EC) for patients with cancer who are receiving myelosuppressive chemotherapy.

The biosimilar is a pegylated growth colony–stimulating factor indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia. It is not indicated for the mobilization of peripheral blood progenitor cells for hematopoietic stem cell transplantation.

In clinical trials, the most common adverse reactions (?5% incidence) are bone pain and pain in extremity.

Full prescribing information is available at www.UDENYCA.com.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/fda-approves-pegfilgrastim-biosimilar>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

November 29, 2018

Sufentanil

(Dsuvia—AcelRx)

New sublingual opioid approved for use in health care settings only

Uses/Notes

On November 2, AcelRx announced FDA approval of [sufentanil](#) for management of acute pain severe enough to require an opioid analgesic for adult patients in certified medically supervised health care settings, such as hospitals, surgical centers, and emergency departments.

It is the first and only sufentanil sublingual tablet approved for acute pain in health care settings and will not be available in retail pharmacies or for outpatient use, according to AcelRx in a news release. Health care settings must be certified in a sufentanil Risk Evaluation and Mitigation Strategy (REMS) program following attestation by an authorized representative that the health care setting will comply with appropriate dispensing and use restrictions.

As part of the REMS program, AcelRx will monitor distribution and audit wholesalers' data, evaluate proper use within the health care settings, and monitor for any diversion and abuse. In addition, AcelRx will decertify health care settings that are noncompliant with the REMS program.

The 30-mcg sufentanil tablet comes in a single-dose, prefilled applicator for sublingual administration.

Approval was based on a randomized, double-blind, placebo-controlled clinical study demonstrating a statistically greater summed pain intensity difference from baseline over the first 12 hours of the study compared with placebo. The pain intensity difference from baseline was superior to that of the placebo group within 15 minutes, and median meaningful pain relief occurred following a single dose.

The single-strength tablet and single-unit packaging are designed to mitigate the possibility of dosing errors, misuse, and diversion. The sublingual administration makes the opioid an option for patients with nothing-by-mouth status and patients with difficult I.V. access (e.g., obese, older adults, burn, needle-phobic).

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/new-sublingual-opioid-approved-use-health-care-settings-only>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

November 29, 2018

Epinephrine inhalation aerosol bronchodilator suspension

Uses/Notes

On November 8, [FDA approved](#) a new version of epinephrine inhalation aerosol bronchodilator suspension—known as Primatene Mist. The OTC metered-dose inhaler was reapproved to provide temporary relief for symptoms of mild, intermittent asthma in those who have been diagnosed with asthma by a health care provider.

The former OTC Primatene Mist was taken off the market in 2011 because it contained chlorofluorocarbon (CFC) propellants, which are known to deplete the ozone layer. This new version contains hydrofluoroalkane (HFAs) propellants, which are permitted under current international and U.S. law. Prescription-only inhalers that use different medications, such as albuterol and levalbuterol, also use HFAs as propellants.

In an FDA news release discussing concerns about the reapproval, FDA Commissioner Scott Gottlieb, MD, and Janet Woodcock, MD, director of the Center for Drug Evaluation and Research, stated that as the [OTC product is being reintroduced](#), the agency has taken steps to make sure consumers understand how to safely and effectively use the new product.

“Health professionals can ensure that patients understand and correctly apply the instructions for use. ... Patients with more severe asthma should not rely on it. Instead, they should be working with their health care provider to ensure an appropriate treatment plan for their condition,” they said. “You’ll see that this risk is addressed in the instructions on how to use the product safely and a warning to seek medical care if the patient is using it regularly as overuse of the product is a risk.”

They also noted that “for the right patient, our analysis of the data, including new information that was developed since this product was previously on the market, shows that there are no serious safety concerns when Primatene Mist is used as directed.” But they pointed out that severe exacerbations can still occur even in individuals with mild asthma and that “any

***(Primatene Mist—Amphastar
Pharmaceuticals)***

**FDA approves new version of Primatene Mist for
mild asthma**

patient who experiences severe exacerbations should go to the emergency department right away."

It's also important to note that the new product looks different from the old version, with updated instructions for use that patients need to follow for the inhaler to work properly, they added.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-new-version-primatene-mist-mild-asthma>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

November 29, 2018

Pembrolizumab

(Keytruda—Merck)

Drug now approved to treat HCC, most common type of liver cancer

Uses/Notes

FDA approved a [new indication for pembrolizumab](#), an anti-PD-1 therapy, for treatment of hepatocellular carcinoma (HCC) in patients who have been previously treated with sorafenib. HCC is the most common type of liver cancer in adults.

The recommended dosage for HCC is 200 mg every 3 weeks until disease progression or unacceptable toxicity.

The humanized monoclonal antibody works by blocking the interaction between PD-1 and its ligands, PD-L1 and PD-L2, thereby activating T lymphocytes, which may affect both tumor cells and healthy cells.

Approval was based on data from a single-arm, open-label, multicenter trial evaluating pembrolizumab in 104 patients with HCC who had disease progression on or after sorafenib or who were intolerant to sorafenib.

Immune-mediated adverse reactions, which may be severe or fatal, can occur with use, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, severe skin reactions, solid organ transplant rejection, and complications of allogeneic hematopoietic stem cell transplantation.

Depending on the severity of the adverse reaction, the drug should be withheld or discontinued and corticosteroids administered if appropriate.

Pembrolizumab can also cause severe or life-threatening infusion-related reactions, as well as fetal harm when administered to a pregnant woman.

Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials, stated Merck in a news release.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/drug-now-approved-treat-hcc-most-common-type-liver-cancer>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

November 29, 2018

Brentuximab vedotin

Uses/Notes

On November 16, [FDA approved](#) brentuximab vedotin injection in combination with chemotherapy for adult patients with certain types of peripheral T-cell lymphoma (PTCL). This is the first FDA approval for treatment of newly diagnosed PTCL, and the agency used a new review program to complete the approval more quickly.

PTCLs are rare, fast-growing non-Hodgkin's lymphomas that develop from T-cells. The T-cells often spread quickly throughout the body and are hard to treat.

Brentuximab vedotin is a monoclonal antibody that binds to a CD30 protein found on some cancer cells.

The drug was previously approved to treat adult patients with previously untreated stage III or IV classical Hodgkin lymphoma (cHL), cHL after relapse, cHL after stem cell transplant when a patient is at a high risk of relapse or progression, systemic ALCL after failure of other treatment, and primary cutaneous ALCL or CD30-expressing mycosis fungoides after failure of other treatment.

The new approval was based on a clinical trial of 452 patients with certain PTCLs who received either brentuximab vedotin plus chemotherapy or a standard chemotherapy (CHOP) as first-line treatment.

The most common adverse effects of brentuximab vedotin plus chemotherapy included nerve damage (peripheral neuropathy), nausea and vomiting, diarrhea, low white blood cell counts, fatigue, mouth sores, constipation, hair loss, fever, and anemia.

Health care providers are advised to monitor patients for infusion reactions, life-threatening allergic reactions, neuropathy, fever, GI complications and infections. Patients should also be monitored for tumor lysis syndrome, serious skin reactions, lung adverse effects, and liver damage.

Women who are pregnant or breastfeeding should not take brentuximab vedotin because it may cause harm to a developing fetus or newborn baby.

(*Adcetris*—Seattle Genetics)

FDA approves expanded use for first-line treatment of peripheral T-cell lymphoma

The prescribing information includes a boxed warning to advise health professionals and patients about the risk of a fatal or life-threatening infection of the brain (progressive multifocal leukoencephalopathy) in patients receiving the drug.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/fda-approves-expanded-use-first-line-treatment-peripheral-t-cell-lymphoma>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

November 29, 2018

Gilteritinib

(Xospata—Astellas Pharma)

New drug targets relapsed or refractory AML in adults with FLT3 mutation

Uses/Notes

FDA [approved](#) gilteritinib tablets to treat relapsed or refractory acute myeloid leukemia (AML) in adult patients with an FLT3 mutation as detected by an FDA-approved test, the LeukoStrat CDx FLT3 Mutation Assay (Invivoscribe Technologies).

Efficacy of gilteritinib was studied in a clinical trial of 138 patients with relapsed or refractory AML having a confirmed FLT3 mutation. Twenty-one percent of patients achieved complete remission (no evidence of disease and full recovery of blood counts) or complete remission with partial hematologic recovery (no evidence of disease and partial recovery of blood counts) with treatment.

Of the 106 patients who required red blood cell or platelet transfusions at the start of treatment, 31% became transfusion-free for at least 56 days.

Common adverse effects reported in clinical trials were muscle and joint pain, fatigue, and elevated liver enzymes.

Health care providers are advised to monitor patients for posterior reversible encephalopathy syndrome, which is characterized by headache, confusion, seizures, and visual loss; prolonged QT interval; and pancreatitis.

Rare cases of differentiation syndrome (symptoms of which may include fever, cough, trouble breathing, fluid around the lungs or heart, rapid weight gain, swelling, and renal or hepatic dysfunction) have been seen in patients taking the drug.

Women who are pregnant or breastfeeding should not take gilteritinib because it may cause harm to a developing fetus or newborn baby.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/new-drug-targets-relapsed-or-refractory-aml-adults-flt3-mutation>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

November 29, 2018

Amifampridine

(Firdapse—Catalyst Pharmaceuticals)

FDA approves first treatment for Lambert-Eaton myasthenic syndrome

Uses/Notes

FDA [approved amifampridine](#) tablets for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults. LEMS is a rare autoimmune disorder that affects the connection between nerves and muscles and causes weakness and other symptoms in affected patients. This is the first FDA approval of a treatment for LEMS.

Efficacy of amifampridine was studied in two clinical trials that together included 64 adult patients who received amifampridine or placebo. The studies measured the Quantitative Myasthenia Gravis score (a 13-item physician-rated categorical scale assessing muscle weakness) and the Subject Global Impression (a 7-point scale on which patients rated their overall impression of the effects of the study treatment on their physical well-being).

For both measures, the patients receiving amifampridine experienced a greater benefit than those on placebo.

The most common adverse effects in the clinical trials were burning or prickling sensation, upper respiratory tract infection, abdominal pain, nausea, diarrhea, headache, elevated liver enzymes, back pain, hypertension, and muscle spasms. Seizures have been observed in patients without a history of seizures.

Patients should inform their health care provider immediately if they have signs of hypersensitivity reactions, such as rash, hives, itching, fever, swelling, or trouble breathing.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-first-treatment-lambert-eaton-myasthenic-syndrome>

Alerts and Recalls

Generic Name (Trade Name—Company)

November 29, 2018

Alemtuzumab

Uses/Notes

FDA is warning that rare but serious cases of stroke and tears in the lining of arteries in the head and neck have occurred in patients with multiple sclerosis (MS) shortly after they received alemtuzumab. These problems can lead to permanent disability and even death.

As a result, the agency has added a new warning about these risks to the prescribing information in the [drug label](#) and to the patient [Medication Guide](#). FDA also added the risk of stroke to the existing boxed warning, its most prominent warning.

Alemtuzumab is also approved under the brand name Campath, which was approved in May 2001 to treat B-cell chronic lymphocytic leukemia (B-CLL). The [Campath drug label](#) will also be updated to include these risks in the adverse reactions section under postmarketing experience.

Patients or their caregivers should seek emergency treatment immediately if the patient experiences signs or symptoms of a stroke or tears in the lining of the head and neck arteries, called arterial dissection, which can include sudden numbness or weakness in the face, arms, or legs, especially if it occurs on only one side of the body; sudden confusion, trouble speaking, or difficulty understanding speech; sudden trouble seeing in one or both eyes; sudden trouble with walking, dizziness, or loss of balance or coordination; and sudden severe headache or neck pain.

Most patients taking alemtuzumab who developed stroke or tears in the artery linings developed symptoms within 1 day of receiving the drug. One patient reported symptoms that occurred 3 days after treatment.

Health professionals should advise patients at every alemtuzumab infusion to seek immediate emergency medical attention if they experience symptoms of ischemic or hemorrhagic stroke or cervicocephalic arterial dissection. The diagnosis is often complicated because early symptoms such as headache and neck pain are not specific. Promptly evaluate patients who complain of symptoms consistent with these conditions.

(Lemtrada—Genzyme)

FDA warns about rare but serious risks of stroke, blood vessel wall tears with MS drug

In the nearly 5 years since FDA approved alemtuzumab in 2014 to treat relapsing forms of MS, the agency has identified 13 worldwide cases of ischemic and hemorrhagic stroke or arterial dissection that occurred shortly after the patient received alemtuzumab. This number includes only reports submitted to FDA, so additional cases the agency is unaware of may have occurred. Twelve of these cases reported symptoms within 1 day of receiving the drug.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/fda-warns-about-rare-serious-risks-stroke-blood-vessel-wall-tears-ms-drug>

Alerts and Recalls

Generic Name (Trade Name—Company)

November 29, 2018

Enasidenib

Uses/Notes

[FDA is warning](#) that signs and symptoms of a life-threatening adverse effect called differentiation syndrome are not being recognized in patients receiving the acute myeloid leukemia medicine enasidenib. The enasidenib [prescribing information](#) and [patient Medication Guide](#) already contain a warning about differentiation syndrome. However, the agency said it has become aware of cases of differentiation syndrome not being recognized and patients not receiving the necessary treatment.

As a result, FDA is alerting health professionals and patients about the need for early recognition and aggressive management of differentiation syndrome to lessen the likelihood of serious illness and death. The agency is continuing to monitor this safety concern.

Health professionals should describe to patients the symptoms of differentiation syndrome listed in the [Medication Guide](#) when starting enasidenib and at follow-up visits, and inform them to call their health professional if such symptoms occur. Differentiation syndrome has occurred as early as 10 days and up to 5 months after starting the medicine. If patients experience unexplained respiratory distress or other symptoms, consider a diagnosis of differentiation syndrome, and treat promptly with oral or I.V. corticosteroids.

Patients should contact their health professional or go to the nearest hospital emergency department right away if they develop any of the following symptoms of differentiation syndrome while taking enasidenib: fever; cough; shortness of breath; swelling of arms and legs; swelling around the neck, groin, or underarm area; fast weight gain of more than 10 pounds within a week; bone pain; or feeling dizzy or lightheaded.

Enasidenib was approved in August 2017 to treat patients with acute myeloid leukemia (AML) with a specific genetic mutation called isocitrate dehydrogenase (IDH)-2 whose disease has come back or has not improved after treatment with other chemotherapy medicines. Enasidenib works by blocking several enzymes that promote this abnormal blood cell

(Idhifa—Celgene)

Health professionals urged to recognize symptoms of life-threatening differentiation syndrome in patients taking leukemia drug

growth.

In the clinical trial conducted for enasidenib's approval, at least 14% of patients experienced differentiation syndrome. The manufacturer's safety report, which included the period of May 1, 2018, to July 31, 2018, reported five cases of death associated with differentiation syndrome in patients taking the drug.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/health-professionals-urged-recognize-symptoms-life-threatening-differentiation>

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