
A^{PhA} **DrugInfoLine[®]**

July 2018

[Cardiology](#)

Advising on this article: Eric MacLaughlin

July 2, 2018

Self-monitoring results in better BP control than clinic-based monitoring

Key Point

Results of a large, 12-month, open-label, multicenter trial in patients with uncontrolled hypertension showed that self-monitoring (SM) of blood pressure (BP) with or without telemonitoring (TM) resulted in better BP control compared with clinic-based BP monitoring. Primary care clinicians were better able to titrate antihypertensive medications to meet recommended goals.

Source URL:

<http://www.aphadruginfoline.com/cardiology/self-monitoring-results-better-bp-control-clinic-based-monitoring>

[Gastroenterology](#)

Advising on this article: C. Wayne Weart

July 2, 2018

Corticosteroids for severe alcoholic hepatitis improves short-term outcomes

Key Point

According to a study published in Gastroenterology, use of corticosteroids in patients with severe alcoholic hepatitis significantly reduced the risk of death within 28 days when compared with controls or pentoxifylline. However, no difference was seen in 6-month mortality for any treatment or controls.

Source URL:

<http://www.aphadruginfoline.com/gastroenterology/corticosteroids-severe-alcoholic-hepatitis-improves-short-term-outcomes>

Focus on Immunizations

Advising on this article: John D. Grabenstein

July 9, 2018

Communication strategies to improve HPV vaccination rates

Key Point

Providers with a persistent communication style that focuses on the benefits of HPV vaccine and a strong recommendation to accept vaccination resulted in much higher same-day vaccination rates compared with acquiescence and agreement to defer the vaccination, according to a study published in Pediatrics.

Source URL:

<http://www.aphadruginfoline.com/focus-immunizations/communication-strategies-improve-hpv-vaccination-rates>

[Cardiology](#)

Advising on this article: Eric MacLaughlin

July 9, 2018

Vitamins and mineral supplements have little benefit on CV outcomes

Key Point

No significant benefits were observed with use of multivitamins, vitamin D, calcium, or vitamin C on cardiovascular (CV) outcomes or all-cause mortality. Only low- to moderate-quality evidence supports use of folic acid to reduce CV disease and folic acid and B vitamins to reduce the risk of stroke, according to results of systematic reviews and meta-analyses published in the Journal of the American College of Cardiology.

Source URL:

<http://www.aphadruginfoline.com/cardiology/vitamins-and-mineral-supplements-have-little-benefit-cv-outcomes>

[Drug Interactions Corner](#)

Advising on this article: Daniel S. Streetman

July 16, 2018

Drug interactions are common among older adults receiving antiretroviral therapies

Key Point

A cross-sectional observational study published in the Journal of Acquired Immune Deficiency Syndromes involving 744 patients with HIV receiving antiretroviral treatment and at least one nonantiretroviral medication showed that more than one-half of these patients had at least one or more potential drug–drug interactions (DDIs), with a higher risk of interactions observed for those receiving five or more medications.

Source URL:

<http://www.aphadruginfoline.com/drug-interactions-corner/drug-interactions-are-common-among-older-adults-receiving-antiretroviral>

[Pharmacogenomics Corner](#)

Advising on this article: Mary W. Roederer

July 16, 2018

Pharmacogenetic-based decision tools are not interchangeable

Key Point

A comparison of four commercially available pharmacogenetic-based decision tools in patients with major depressive disorder (MDD) and numerous treatment failures showed that genotype and predicted phenotype agreement varied substantially, as did medication recommendations, indicating these tests cannot be considered equivalent or interchangeable.

Source URL:

<http://www.aphadruginfoline.com/pharmacogenomics-corner/pharmacogenetic-based-decision-tools-are-not-interchangeable>

[Alerts and Recalls](#)

Generic Name (Trade Name—Company)

July 9, 2018

Celecoxib

Uses/Notes

FDA approved a [labeling supplement](#) for celecoxib, a COX-2 selective NSAID, to include results from a postmarketing cardiovascular outcomes trial that found that at the lowest dose, cardiovascular safety of celecoxib was similar to that of moderate doses of naproxen and ibuprofen.

Concerns about the cardiovascular thrombotic risk of COX-2 selective NSAIDs emerged in the early 2000s. Following an FDA Advisory Committee meeting held in 2005, which considered data from large clinical outcome trials in a wide range of indications and epidemiology studies of several individual NSAIDs, FDA concluded that the risk for cardiovascular thrombotic events was present for both COX-2 selective NSAIDs and nonselective NSAIDs.

The Prospective Randomized Evaluation of Celecoxib Integrated Safety vs Ibuprofen or Naproxen (PRECISION) trial was conducted to address the remaining concerns about the relative cardiovascular safety of COX-2 selective NSAIDs and nonselective NSAIDs. PRECISION was a large, randomized, double-blind controlled trial that began in 2006. Ninety percent of the patients enrolled in the trial had osteoarthritis, and the remaining 10% had rheumatoid arthritis.

Results of the PRECISION trial demonstrated that celecoxib at the lowest approved dose of 100 mg twice daily is noninferior to (or no worse than) ibuprofen dosed in the range of 600 mg to 800 mg three times daily or naproxen dosed in the range of 375 mg to 500 mg twice daily on a composite cardiovascular endpoint consisting of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

In an ambulatory blood pressure monitoring study that was part of the larger PRECISION trial, celecoxib dosed at 100 mg twice daily showed little effect on average 24-hour systolic blood pressure (SBP), whereas ibuprofen dosed in the range of 600 mg to 800 mg three times daily and naproxen dosed in the range of 375 mg to 500 mg twice daily increased average 24-hour SBP

(Celebrex—Pfizer)

At lowest dose, CV safety similar to moderate doses of naproxen, ibuprofen

by 3.7 mmHg and 1.6 mmHg, respectively.

Too few patients received higher doses of celecoxib to evaluate the risk of cardiovascular events or the effect on blood pressure for doses greater than 100 mg twice daily. The cardiovascular risks of the NSAID class are dose dependent; therefore, the results for celecoxib 100 mg twice daily on the composite cardiovascular endpoint and the lack of effect on SBP cannot be extrapolated to dosing regimens using the higher strengths of celecoxib (200 mg or 400 mg).

Patients with recent cardiovascular events such as acute MI, coronary revascularization, or coronary stent placement were not studied in the PRECISION trial. NSAID class labeling warns against use of NSAIDs in such patients.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/lowest-dose-cv-safety-similar-moderate-doses-naproxen-ibuprofen>

[Alerts and Recalls](#)

Generic Name (Trade Name—Company)

July 9, 2018

Neostigmine methylsulfate 5-mL syringes

(No trade names—Fagron Sterile Services)

Two lots of recalled syringe units may be incorrectly labeled

Uses/Notes

Fagron Sterile Services is voluntarily [recalling two lots](#) of neostigmine methylsulfate 5-mL syringes because some syringe units containing 1 mg/mL, 5 mg per 5mL, are incorrectly labelled as 1 mg/mL, 3 mg per 3mL. Secondary packages are properly labelled as neostigmine methylsulfate 1 mg/mL, 5 mg per 5mL.

If 5 mL rather than the intended 3mL is administered to a patient, adverse events overdosage can range from nausea, vomiting, diarrhea, excessive salivation and sweating, increased bronchial secretions, miosis, bradycardia or tachycardia, cardiospasm, bronchospasm, incoordination, muscle cramps, fasciculation, and paralysis, to cholinergic crisis resulting in death.

To date, Fagron has not received any reports of adverse events or injuries related to this recall.

Neostigmine methylsulfate injection is a cholinesterase inhibitor indicated for reversal of the effects of nondepolarizing neuromuscular blocking agents after surgery.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/two-lots-recalled-syringe-units-may-be-incorrectly-labeled>

[Alerts and Recalls](#)

Generic Name (Trade Name—Company)

July 9, 2018

Kratom products

(Blissful Remedies—World Organix LLC)

Recalled kratom products are contaminated with high counts of bacteria

Uses/Notes

[FDA is advising](#) consumers not to use kratom products sold by World Organix LLC, Las Vegas, NV. FDA laboratory analysis found that the products are contaminated with high counts of various bacteria that can cause infections, including salmonella, *Clostridium difficile*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*.

The products were [recalled](#) on June 30, 2018; however, FDA is concerned this recall does not include all lot numbers of the affected products.

FDA has received [reports of adverse events](#) associated with kratom products. The agency strongly discourages the public from consuming kratom, as there are no proven medical uses for kratom, an inherently addictive product that can cause harm.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/recalled-kratom-products-are-contaminated-high-counts-bacteria>

Supplemental Approvals

Generic Name (Trade Name—Company)

July 9, 2018

Encorafenib, binimetinib

(*Braftovi*, *Mektovi*—Array BioPharma)

Agents approved in combination for unresectable or metastatic melanoma with BRAF mutations

Uses/Notes

FDA approved [encorafenib and binimetinib](#) in combination for patients with unresectable or metastatic melanoma with a *BRAF V600E* or *V600K* mutation, as detected by an FDA-approved test.

Approval was based on a randomized, active-controlled, open-label, multicenter trial in 577 patients with *BRAF V600E* or *V600K* mutation-positive unresectable or metastatic melanoma. Patients were randomized (1:1:1) to receive binimetinib 45 mg twice daily plus encorafenib 450 mg once daily, encorafenib 300 mg once daily, or vemurafenib 960 mg twice daily. Treatment continued until disease progression or unacceptable toxicity.

The major efficacy measure was progression-free survival (PFS) using RECIST 1.1 response criteria and assessed by blinded independent central review. The median PFS was 14.9 months for patients receiving binimetinib plus encorafenib and 7.3 months for the vemurafenib monotherapy arm (hazard ratio 0.54 [95% CI 0.41–0.71], $P < 0.0001$). Overall response rates assessed by central review were 63% and 40%, respectively. Median response duration was 16.6 months vs. 12.3 months, respectively.

The most common (>25%) adverse reactions in patients receiving the combination were fatigue, nausea, diarrhea, vomiting, abdominal pain, and arthralgia. Discontinuation of therapy due to adverse reactions occurred in 5% of patients receiving the combination; the most common reasons were hemorrhage and headache.

FDA also granted approval of the THxID BRAF Kit (bioMérieux) as a companion diagnostic for these therapeutics.

The recommended doses are binimetinib 45 mg orally twice daily and encorafenib 450 mg orally once daily.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/agents-approved-combination-unresectable-or-metastatic-melanoma-braf>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

July 9, 2018

Glycopyrronium

(Qbrexza—Dermira)

FDA approves first once-daily, topical prescription for excessive underarm sweating

Uses/Notes

Dermira announced FDA [approval of glycopyrronium](#) cloth, an anticholinergic indicated for topical treatment of primary axillary hyperhidrosis in adult and pediatric patients aged 9 years and older.

Commonly known as excessive underarm sweating, primary axillary hyperhidrosis is a chronic medical skin condition that results in sweating beyond what is needed for normal body temperature regulation. The exact cause is unknown, but it affects nearly 10 million people in the United States, with both men and women having similar prevalence. Approved under the trade name Qbrexza (pronounced kew brex' zah), it is applied directly to the skin and is designed to block sweat production by inhibiting sweat gland activation.

Approval was based on [results](#) from two Phase III clinical trials, ATMOS-1 and ATMOS-2, which evaluated the efficacy and safety of Qbrexza in patients with primary axillary hyperhidrosis. Both trials assessed the absolute change from baseline in sweat production (the weight or amount of sweat a patient produced) following treatment with Qbrexza and the proportion of patients who achieved at least a four-point improvement from baseline in their sweating severity, as measured by the Axillary Sweating Daily Diary (ASDD), Dermira's proprietary patient-reported outcome (PRO) instrument.

The most common adverse effects observed following topical application of Qbrexza to the underarms were dry mouth, dilated pupil, sore throat, headache, urinary hesitation, blurred vision, dry nose, dry throat, dry eye, dry skin, and constipation. The most common local skin reactions were erythema, burning/stinging, and pruritus.

Qbrexza is expected to be available nationwide in pharmacies beginning in October 2018. For more information, visit www.qbrexza.com.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-first-once-daily-topical-prescription-excessive-underarm-sweating>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

July 9, 2018

Incobotulinumtoxin A

(Xeomin—Merz North America)

First neurotoxin approved for chronic sialorrhea, or excessive drooling

Uses/Notes

FDA approved [incobotulinumtoxinA](#) to treat chronic sialorrhea, or excessive drooling, in adult patients. It is the first and only neurotoxin with this approved indication in the United States.

Sialorrhea is a common symptom among patients who have neurological disorders such as Parkinson disease, amyotrophic lateral sclerosis, or cerebral palsy or who have had a stroke. The condition can occur from difficulty retaining saliva inside the mouth, from issues with swallowing, and from problems controlling facial muscles.

Approval for this indication was based on a Phase III, randomized, double-blind, placebo-controlled, multicenter trial involving 184 patients in which both coprimary endpoints were successfully achieved. Study participants received placebo (n = 36), incobotulinumtoxinA 75 U (n = 74), or incobotulinumtoxinA 100 U (n = 74). Overall frequency of adverse events was similar between placebo and treatment groups, with no new or unexpected adverse events reported.

This is the fourth neurological indication for the neurotoxin, which was first approved by FDA in 2010 to treat cervical dystonia and blepharospasm (in patients previously treated with onabotulinumtoxinA) in adult patients and later in 2015 for upper limb spasticity in adult patients.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/first-neurotoxin-approved-chronic-sialorrhea-or-excessive-drooling>

[New Drug Approvals](#)

Generic Name (Trade Name—Company)

July 16, 2018

Tecovirimat

(Tpoxx—SIGA Technologies)

FDA approves first drug with an indication for treatment of smallpox

Uses/Notes

FDA has approved [tecovirimat](#), the first drug with an indication for treatment of smallpox. Though the World Health Organization declared smallpox, a contagious and sometimes fatal infectious disease, eradicated in 1980, there have been longstanding concerns that smallpox could be used as a bioweapon.

Prior to its eradication in 1980, variola virus, the virus that causes smallpox, was mainly spread by direct contact between people. Symptoms typically began 10 to 14 days after infection and included fever, exhaustion, headache, and backache. A rash initially consisting of small, pink bumps progressed to pus-filled sores before finally crusting over and scarring. Complications of smallpox could include encephalitis (inflammation of the brain), corneal ulcerations (an open sore on the clear, front surface of the eye) and blindness.

Tecovirimat's effectiveness against smallpox was established by studies conducted in animals infected with viruses that are closely related to the virus that causes smallpox and was based on measuring survival at the end of the studies. More animals treated with tecovirimat lived compared with the animals treated with placebo.

It was approved under the FDA's Animal Rule, which allows efficacy findings from adequate and well-controlled animal studies to support an FDA approval when it is not feasible or ethical to conduct efficacy trials in humans.

Safety of the agents was evaluated in 359 healthy human volunteers without a smallpox infection. The most frequently reported adverse effects were headache, nausea, and abdominal pain.

Source URL:

<http://www.aphadruginfoline.com/new-drug-approvals/fda-approves-first-drug-indication-treatment-smallpox>

Alerts and Recalls

Generic Name (Trade Name—Company)

July 16, 2018

Valsartan

Uses/Notes

[FDA is alerting](#) health professionals and patients of a voluntary recall of several drug products containing the active ingredient valsartan, used to treat high blood pressure and heart failure. This recall is due to an impurity, N-nitrosodimethylamine (NDMA), which was found in the recalled products. However, not all products containing valsartan are being recalled. NDMA is classified as a probable human carcinogen based on results from laboratory tests. The presence of NDMA was unexpected and is thought to be related to changes in the way the active substance was manufactured.

FDA's review is ongoing and has included investigating the levels of NDMA in the recalled products, assessing the possible effect on patients who have been taking them and what measures can be taken to reduce or eliminate the impurity from future batches produced by the company.

Because valsartan is used in medicines to treat serious medical conditions, patients taking the recalled valsartan-containing medicines should continue taking their medicine until they have a replacement product. To determine whether a specific product has been recalled, patients should look at the drug name and company name on the label of their prescription bottle. If the information is not on the bottle, patients should contact the pharmacy that dispensed the medicine. If a patient is taking one of the recalled medicines, they should follow the recall instructions provided by the specific company. This information will be posted to the FDA's [website](#).

Patients should also contact their health professional (the pharmacist who dispensed the medication or doctor who prescribed the medication) if their medicine is included in this recall to discuss their treatment, which may include another valsartan product not affected by this recall or an alternative treatment option.

The companies listed are recalling all lots of nonexpired products that contain the ingredient valsartan supplied by a third party. Not all valsartan-containing medicines distributed in the United States have valsartan active pharmaceutical ingredient (API) supplied by this specific

(Multiple trade names—Multiple companies)

FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity

company. The supplier has stopped distributing its valsartan API, and FDA is working with the affected companies to reduce or eliminate the valsartan API impurity from future products.

FDA will continue to investigate this issue and provide additional information when it becomes available.

Source URL:

<http://www.aphadruonline.com/alerts-and-recalls/fda-announces-voluntary-recall-several-medicines-containing-valsartan-following>

Alerts and Recalls

Generic Name (Trade Name—Company)

July 16, 2018

Fluoroquinolone antibiotics

Uses/Notes

[FDA is strengthening](#) the current warnings in the prescribing information that fluoroquinolone antibiotics may cause significant decreases in blood glucose and certain mental health adverse effects. The low blood glucose levels can result in serious problems, including coma, particularly in older people and patients with diabetes who are taking medications to reduce blood glucose levels.

The agency announced it is making these changes because a recent review found reports of life-threatening low blood glucose adverse effects and reports of additional mental health adverse effects.

FDA is requiring these updates in the [drug labels](#) and to the patient [Medication Guides](#) for the entire class of fluoroquinolones (see List of FDA-Approved Fluoroquinolones for Systemic Use). This affects only the fluoroquinolone formulations taken by mouth or given by injection. Blood glucose disturbances, including high blood and low blood glucose levels, are already included as a warning in most fluoroquinolone drug labels; however, FDA is adding that low blood glucose levels (hypoglycemia) can lead to coma.

Across the fluoroquinolone antibiotic class, a range of mental health adverse effects are already described under Central Nervous System Effects in the Warnings and Precautions section of the drug label, which differed by individual drug. The new label changes will make the mental health adverse effects more prominent and more consistent across the systemic fluoroquinolone drug class.

The mental health adverse effects to be added to or updated across all the fluoroquinolones are disturbances in attention, disorientation, agitation, nervousness, memory impairment, and serious disturbances in mental abilities (delirium).

Patients should tell their health professionals if they are taking a diabetes medicine when their health professional is considering prescribing an antibiotic, and also if they have low blood glucose or symptoms of it

(Multiple trade names—Multiple companies)

FDA announces label changes, reissues warnings about fluoroquinolone antibiotics

while taking a fluoroquinolone. Health professionals may ask patients with diabetes to check their blood glucose levels more often while taking a fluoroquinolone.

Health professionals should be aware of the potential risk of hypoglycemia sometimes resulting in coma, occurring more frequently in older adults and those with diabetes taking an oral hypoglycemic medicine or insulin. Alert patients of the symptoms of hypoglycemia, carefully monitor blood glucose levels in these patients, and discuss with them how to treat themselves if they have symptoms of hypoglycemia. Inform patients about the risk of psychiatric adverse reactions that can occur after just one dose.

Stop fluoroquinolone treatment immediately if a patient reports any central nervous system adverse effects, including psychiatric adverse reactions, or blood glucose disturbances, and switch to a nonfluoroquinolone antibiotic if possible. Stop fluoroquinolone treatment immediately if a patient reports serious adverse effects involving the tendons, muscles, joints, or nerves, and switch to a nonfluoroquinolone antibiotic to complete the patient's treatment course.

Health professionals should not prescribe fluoroquinolones to patients who have other treatment options for acute [bacterial sinusitis \(ABS\)](#), [acute bacterial exacerbation of chronic bronchitis \(ABECB\)](#), [and uncomplicated urinary tract infections \(uUTI\)](#) because the risks outweigh the benefits in these patients.

Source URL:

<http://www.aphadruginfoline.com/alerts-and-recalls/fda-announces-label-changes-reissues-warnings-about-fluoroquinolone-antibiotics>

Supplemental Approvals

Generic Name (Trade Name—Company)

July 19, 2018

Ribociclib

(Kisqali—Novartis)

FDA expands use of breast cancer drug

Uses/Notes

[FDA approved ribociclib](#) in combination with an aromatase inhibitor for the treatment of pre/perimenopausal or postmenopausal women with hormone receptor (HR)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced or metastatic breast cancer, as initial endocrine-based therapy.

FDA also approved ribociclib in combination with fulvestrant for the treatment of postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer, as initial endocrine based therapy or following disease progression on endocrine therapy.

This is the first approval that FDA has granted as part of two new pilot programs announced earlier this year that collectively aim to make the development and review of cancer drugs more efficient, while improving FDA’s rigorous standard for evaluating efficacy and safety. With this real-time review, FDA was able to start evaluating the clinical data as soon as the trial results become available, enabling FDA to be ready to approve the new indication upon filing of a formal application with the agency.

Currently the two pilot programs are being used for supplemental applications for already approved cancer drugs and could later be expanded to original drugs and biologics.

Ribociclib was first approved in March 2017 for use with an AI to treat HR-positive, HER2-negative breast cancer in postmenopausal women whose cancer is advanced or has spread to other parts of the body.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/fda-expands-use-breast-cancer-drug>

[Supplemental Approvals](#)

Generic Name (Trade Name—Company)

July 19, 2018

Darunavir, cobicistat, emtricitabine, tenofovir alafenamide

(Symtuza—Janssen)

**First once-daily, darunavir-based single-tablet
regimen approved for treatment of HIV 1 infection**

Uses/Notes

[Janssen announced](#) FDA approval of darunavir 800 mg, cobicistat 150 mg, emtricitabine 200 mg, and tenofovir alafenamide 10 mg under the trade name Symtuza—the first and only complete, darunavir-based single-tablet regimen (STR) for the treatment of HIV-1 in treatment-naïve and certain virologically suppressed adults.

Symtuza combines the high barrier to resistance of darunavir with a formulation designed for improved tolerability and the convenience of an STR.

Approval was based on data from two 48-week, noninferiority, pivotal Phase III studies that assessed the safety and efficacy of Symtuza versus a control regimen in adults with no prior antiretroviral history (AMBER) and in virologically suppressed adults (EMERALD).

Results from both trials demonstrated that Symtuza was effective and well tolerated, with up to 95% achieving or maintaining virologic suppression (HIV-1 RNA < 50 c/mL).

The recommended dosage of Symtuza is one tablet taken once daily with food. Symtuza is not recommended in patients with creatinine clearance below 30 mL per minute or those with severe hepatic impairment.

According to the prescribing information, prior to or when initiating treatment with Symtuza, patients should be tested for hepatitis B virus (HBV) infection and renal function, and renal function should be monitored as clinically appropriate during therapy. The agent comes with a boxed warning on the risk of posttreatment acute exacerbation of hepatitis B.

Source URL:

<http://www.aphadruginfoline.com/supplemental-approvals/first-once-daily-darunavir-based-single-tablet-regimen-approved-treatment-hiv>

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