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This continuing education (CE) offering is intended for all pharmacists in the U.S.

Index:

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Release Date: January 21, 2020
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Featuring:

- FDA warns about rare but severe lung inflammation with Ibrance, Kisqali, and Verzenio for breast cancer
- FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease
- FDA review finds no increased risk of prostate cancer with Parkinson's disease medicines containing entacapone (Comtan, Stalevo)
- FDA approves Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR)
- FDA adds Boxed Warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines
- FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering
- FDA adds Boxed Warning for increased risk of death with gout medicine Uloric (febuxostat)
- FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR)

Program Title: **FDA Drug Safety Communications - 2020**

Target Audience: Pharmacists

ACPE Program No.: 0487-0000-19-003-H05-P (knowledge-based activity)

Accreditations: This CE activity is ACPE-accredited for 2.0 contact hours, or 0.20 C.E.U.'s, of patient safety CE (topic designator "05").

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Estimated Time to Complete the Activity: 120 minutes

Procedures: To receive a credit for completing this activity, pharmacy professionals must supply your CPE Monitor ID and month/day of birth. Other procedures are to read this program, complete the post-test questions and evaluation questions on the Answer Sheet, and either:

i) mail the Answer Sheet and the program fee to us. You will receive a Feedback Statement mailed to you within two weeks. Checks or money orders are encouraged. Mail to: Select CE, P.O. Box 21186, Columbus, Ohio 43221- 0186;

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A minimum score of 70% on the post-test is also required to earn credit.

Faculty: Patti Nussle, R.Ph., J.D., is a healthcare attorney who has written and published continuing education programs in pharmacy law and nursing law for healthcare professionals since 2001. Robyn Satterfield, PharmD, is our peer reviewer.

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Objective #1: At the conclusion of this program, participants should be able to list 7 rare but serious events, and their associated drugs, for which the FDA issued Drug Safety Communications in 2019.

Contact Us: By phone (614) 481-8711 or email at patti@selectce.org.

Thank you! We truly enjoy serving you!

Introduction

The U.S. Food and Drug Administration (FDA)'s Drug Safety Communications website was developed to provide healthcare professionals and the public with easy access to important drug safety information. The webpage contains the most recent Drug Safety Communications from FDA as well as links for Early Communications, Follow-Up Early Communications, Information for Healthcare Professional sheets, and Public Health Advisories.

In this continuing education (CE) activity, we bring you the FDA's Drug Safety Communications for 2019. The information is taken directly from the FDA's website where you can find additional information.

FDA warns about rare but severe lung inflammation with Ibrance, Kisqali, and Verzenio for breast cancer[1]

[9-13-2019] The U.S. Food and Drug Administration (FDA) is warning that Ibrance (palbociclib), Kisqali (ribociclib), and Verzenio (abemaciclib) used to treat some patients with advanced breast cancers may cause rare but severe inflammation of the lungs. We have approved new warnings about this risk to the prescribing information and Patient Package Insert for the entire class of these cyclin-dependent kinase 4/6

Question 1:

Ibrance (palbociclib), Kisqali (ribociclib), and Verzenio (abemaciclib) may cause:

a. advanced breast cancer;
b. advanced liver disease;
c. rare but severe inflammation of the lungs;
d. all of the above are true.

1 https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-severe-lung-inflammation-ibrance-kisqali-and-verzenio-breast-cancer

(CDK 4/6) inhibitor medicines. The overall benefit of CDK 4/6 inhibitors is still greater than the risks when used as prescribed.

CDK 4/6 inhibitors are a class of prescription medicines that are used in combination with hormone therapies to treat adults with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative advanced or metastatic breast cancer that has spread to other parts of the body. CDK 4/6 inhibitors block certain molecules involved in promoting the growth of cancer cells. FDA approved Ibrance in 2015, and both Kisqali and Verzenio in 2017. CDK 4/6 inhibitors have been shown to improve the amount of time after the start of treatment the cancer does not grow substantially and the patient is alive, called progression-free survival (**See List of FDA-Approved CDK 4/6 Inhibitors below**).

Patients should notify your health care professional right away if you have any new or worsening symptoms involving your lungs, as they may indicate a rare but life-threatening condition that can lead to death. Symptoms to watch for include:

- Difficulty or discomfort with breathing
- Shortness of breath while at rest or with low activity

Do not stop taking your medicine without first talking to your health care professional. All medicines have side effects even when used correctly as prescribed, but in general the benefits of taking these medicines outweigh these risks. It is important to know that people respond differently to all medicines depending on their health, the diseases they have, genetic factors, other medicines they are taking, and many other factors. Specific risk factors to determine how likely it is that a particular person will experience severe lung inflammation when taking Ibrance, Kisqali, or Verzenio have not been identified.

Health care professionals should monitor patients regularly for pulmonary symptoms indicative of interstitial lung disease (ILD) and/or pneumonitis. Signs and symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams in patients in whom infectious, neoplastic, and other causes have been excluded. Interrupt CDK 4/6 inhibitor treatment in patients who have new or worsening

respiratory symptoms, and permanently discontinue treatment in patients with severe ILD and/or pneumonitis.

We reviewed CDK 4/6 inhibitors cases from completed and ongoing clinical trials undertaken by manufacturers and their postmarket safety databases that described specific types of inflammation of the lungs, called interstitial lung disease and pneumonitis. Across the entire drug class, there were reports of serious cases, including fatalities.

Question 2:

Ibrance (palbociclib), Kisqali (ribociclib), and Verzenio (abemaciclib) may cause:

a. difficulty or discomfort with breathing;
b. shortness of breath while at rest or with low activity;
c. interstitial lung disease (ILD) and pneumonitis;
d. all of the above are true.

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving these or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.[2]

List of FDA-Approved CDK 4/6 Inhibitors

Brand Name	Active Ingredient(s)
Ibrance	palbociclib
Kisqali	ribociclib
Kisqali Femara Co-Pack	ribociclib and letrozole
Verzenio	abemaciclib

2 855-543-DRUG (3784) and press 4 or druginfo@fda.hhs.gov

Data Summary. FDA reviewed cases of interstitial lung disease (ILD) and pneumonitis with cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors that were identified in the manufacturers' completed and ongoing clinical trials and their postmarket safety databases. Although rare, there were

Question 3:

The risk of fatal ILD/pneumonitis in clinical trials of Ibrance (palbociclib), Kisqali (ribociclib), and Verzenio (abemaciclib) was:

a. 10%;
b. 1 – 3%;
c. less than 1%;
d. zero.

serious cases and/or deaths with Ibrance (palbociclib), Verzenio (abemaciclib), and Kisqali (ribociclib). Across clinical trials of the 3 CDK 4/6 inhibitors, 1 to 3 percent of patients had ILD/pneumonitis of any grade and less than 1 percent had fatal outcomes. Among patients who developed ILD/pneumonitis, including fatal cases, there were patients who had no risk factors for lung disease, but some patients had at least one risk factor.

FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease[3]

[08-28-2019] The Food and Drug Administration (FDA) has received reports that the use of Mavyret, Zepatier, or Vosevi to treat chronic hepatitis C in patients with moderate to severe liver impairment has resulted in rare cases of worsening liver function or liver failure. All these medicines contain a hepatitis C virus (HCV) protease inhibitor and are not indicated for use in patients with moderate to severe liver

3 https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and

Question 4:

Mavyret, Zepatier, and Vosevi contain a _____ and are not indicated for use in patients with moderate to severe liver impairment.

a. hepatitis B virus;
b. hepatitis C virus;
c. hepatitis C virus (HCV) protease inhibitor;
d. hepatitis C virus (HCV) protease inhibitor with antibiotic.

impairment. In most patients, symptoms resolved or new onset worsening of liver function improved after stopping the medicine. These medicines have been widely used and are safe and effective in patients with no or mild liver impairment.

In many of the reported cases, liver failure occurred in patients who had signs and symptoms of moderate to severe liver impairment (Child-Pugh B or C) or other serious liver problems and should not have been treated

Question 5:

Liver failure occurred in some patients taking Mavyret, Zepatier, or Vosevi who had:

a. signs and symptoms of moderate to severe liver impairment;
b. other serious liver problems and should not have been treated with these medicines;
c. pre-existing risk factors such as liver cancer or alcohol abuse;
d. all of the above are true.

with these medicines. In some cases, patients were reported to have no cirrhosis or compensated cirrhosis with mild liver impairment (Child-Pugh A) despite having evidence of decreased platelets at baseline or an increase in the pressure within the portal vein that carries blood from the digestive organs to the liver. In addition, some cases had other significant pre-existing risk factors such as liver cancer, alcohol abuse, or serious medical illnesses associated with serious liver problems. These factors may have contributed to clinical worsening of liver function or liver failure during treatment with these hepatitis C medicines. In most cases, liver failure or decompensation typically occurred within the first 4 weeks of starting treatment. We will continue to monitor this safety concern and will communicate any new information to the public if it becomes available.

Mavyret, Zepatier, and Vosevi are FDA-approved to treat chronic hepatitis C in patients without liver impairment or with mild liver impairment (Child-Pugh A). Clinical trials in patients with compensated cirrhosis or mild liver impairment (Child-Pugh A) have shown that these medicines are well tolerated and highly effective. These medicines reduce the amount of HCV in the body by preventing it from multiplying, which over time leads to clearing the virus from the body, or HCV cure, which can prevent or limit liver damage from HCV. HCV is a contagious disease, and without treatment it can lead to serious liver problems, including cirrhosis, liver cancer, and death. When prescribed as indicated, these medicines continue to be safe and effective.

Health care professionals should continue to prescribe Mavyret, Zepatier, or Vosevi as indicated in the prescribing information for patients without liver impairment or with mild liver impairment (Child-Pugh A). Assess severity of liver disease at baseline and closely monitor for signs and symptoms of worsening liver function such as increases in liver enzymes, jaundice, ascites, encephalopathy, and variceal hemorrhage. Assessment of baseline liver disease and close monitoring are especially important in those with pre-existing significant liver problems or risk factors, such as hepatocellular carcinoma or alcohol abuse, which can also contribute to clinical worsening of liver function or liver failure during treatment. Discontinue these medicines in patients who develop signs and symptoms of liver decompensation or as clinically indicated. Mavyret and Zepatier should not be prescribed in patients with any history of prior hepatic decompensation. Vosevi is

indicated for patients who have previously failed certain other HCV treatments and is not recommended in patients with any history of hepatic decompensation unless the benefits outweigh the risk of liver injury, liver failure or death.

Patients should be aware that the risk of serious liver injury is rare. However, you should contact your health care professional right away if you develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools as these may be signs of liver injury. If you have liver impairment or other pre-existing risk factors that can worsen liver function such as a history of alcohol abuse, you should talk with your health care professional about the benefits and risks of the medicine. Do not stop taking these medicines without first talking with your health care professionals because stopping treatment early can lead to inadequate treatment, which could allow your HCV to come back. Over time, this could result in progression to severe liver disease and its complications, including cirrhosis, liver cancer, and death. These medicines have been widely used and are safe and effective in patients without liver impairment or in those with mild liver impairment for whom they are indicated.

We identified 63 cases of worsening liver function called liver decompensation with regimens Mavyret, Zepatier, and Vosevi to treat

Question 6:

In most cases, liver failure or decompensation typically occurred in some patients taking Mavyret, Zepatier, or Vosevi:

a. within the first 48 hours of starting treatment;
b. within the first 4 weeks of starting treatment;
c. after the patients resumed alcohol use;
d. after the patients were diagnosed with liver cancer.

hepatitis C. Some of these cases led to liver failure and death. Most of

these patients had moderate to severe liver impairment and should not have been prescribed these medicines. This number includes only cases submitted to FDA or those found in the medical literature, so there may be additional cases about which we are unaware. In 2018, an estimated 72,000 patients received dispensed prescriptions for Mavyret, Zepatier, or Vosevi from U.S. outpatient retail and mail-order/specialty pharmacies.

FDA review finds no increased risk of prostate cancer with Parkinson's disease medicines containing entacapone (Comtan, Stalevo)[4]

[08-13-2019] A U.S. Food and Drug Administration (FDA) review of additional data found no increased risk of prostate cancer with the use of entacapone to treat Parkinson's disease. We conducted this review after an earlier trial suggested this possible risk. As a result, our recommendations for using Comtan (entacapone) and Stalevo (a combination of entacapone, carbidopa, and levodopa) will remain the same in the prescribing information.

We alerted the public in March 2010 that we were aware of a clinical trial suggesting a possible increased risk of prostate cancer with the entacapone component of Stalevo. We subsequently required the Stalevo manufacturer, Novartis, to conduct a study to further evaluate this potential risk. We also studied this issue independently using data from the Department of Veterans Affairs health care system. Based on these additional studies, we concluded that entacapone use is not associated with an increased risk of prostate cancer.

Medicines that contain entacapone with carbidopa and levodopa have been shown to effectively treat symptoms of Parkinson's disease such as muscle stiffness, tremors, spasms, and poor muscle control. These medicines have been approved and on the market for almost 20 years. The combination of entacapone with carbidopa and levodopa in Stalevo has been shown to reduce end-of-dose "wearing-off" in patients with

4 https://www.fda.gov/drugs/drug-safety-and-availability/fda-review-finds-no-increased-risk-prostate-cancer-parkinsons-disease-medicines-containing

Parkinson's disease to a greater degree than with entacapone alone or with the two-drug combination of carbidopa and levodopa.

Health care professionals should follow standard prostate cancer screening recommendations for patients.

Patient and caregivers should continue to take your medicine as prescribed. Talk to your health care professionals if you have any questions or concerns.

Question 7:

The FDA alerted the public in March 2010 of:

a. a possible increased risk of prostate cancer with the entacapone component of Stalevo;
b. a probable increased risk of all cancers in people taking Stalevo (a combination of entacapone, carbidopa, and levodopa) or Comtan (entacapone);
c. removal of Stalevo from the market;
d. removal of all drugs to treat Parkinson's disease from the market.

Question 8:

The FDA alerted the public in August 2019 that:

a. data from the Department of Veterans Affairs health system found an association between prostate cancer and Comtan or Stalevo;
b. its review of additional data found no increased risk of prostate cancer with the use of entacapone to treat Parkinson's disease;
c. its review of additional data found no symptom improvement with the use of Comtan or Stalevo;
d. Comtan and Stalevo have been removed from the market.

FDA approves Boxed Warning about increased risk of blood clots and death with higher dose of arthritis and ulcerative colitis medicine tofacitinib (Xeljanz, Xeljanz XR)[5]

This is an update to the FDA Drug Safety Communication: *Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to investigate* issued on February 25, 2019.

[7-26-2019] The U.S. Food and Drug Administration has approved new warnings about an increased risk of blood clots and of death with the 10 mg twice daily dose of tofacitinib (Xeljanz, Xeljanz XR), which is used in patients with ulcerative colitis. In addition, the approved use of tofacitinib for ulcerative colitis will be limited to certain patients who are not treated effectively or who experience severe side effects with certain other medicines. We approved these changes, including adding our most prominent *Boxed Warning*, after reviewing interim data from an ongoing safety clinical trial of tofacitinib in patients with rheumatoid arthritis (RA) that examined a lower and this higher dose of the medicine.

The 10 mg twice daily dose of tofacitinib is not approved for RA or psoriatic arthritis (PsA). This dose is only approved for ulcerative colitis for initial treatment and for long-term use in limited situations. While the increased risks of blood clots and of death were seen in patients taking this dose for RA, these risks may also apply to those taking tofacitinib for ulcerative colitis.

Tofacitinib works by decreasing the activity of the immune system; an overactive immune system contributes to RA, PsA, and ulcerative colitis. Tofacitinib was first approved in 2012 to treat adult patients with RA who did not respond well to the medicine methotrexate. In RA, the body attacks its own joints, causing pain, swelling, and loss of function. In 2017, we approved the medicine to treat patients with a second condition that causes joint pain and swelling, PsA, who did not respond well to methotrexate or other similar medicines. In 2018, we approved tofacitinib to treat ulcerative colitis, which is a chronic, inflammatory disease affecting the colon.

5 https://www.fda.gov/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and

Patients should tell your health care professionals if you have a history of blood clots or heart problems and talk to them about any questions or concerns. Stop taking tofacitinib and seek emergency medical attention right away if you experience any unusual symptoms, including those that may signal a blood clot such as:

- Sudden shortness of breath
- Chest pain that worsens with breathing
- Swelling of a leg or arm
- Leg pain or tenderness, or red or discolored skin in the painful or swollen leg or arm

Do not stop taking tofacitinib without first talking to your health care professional, as doing so can worsen your condition.

Question 9:

Regarding Xeljanz and Xeljanz XR, the FDA's new Boxed Warning about an increased risk of blood clots and death is for patients taking:

a. any dose;
b. the 10mg twice daily dose;
c. the 5mg twice daily dose;
d. a 5mg once daily dose.

Health care professionals should discontinue tofacitinib and promptly evaluate patients with symptoms of thrombosis. Counsel patients about the risks and advise them to seek medical attention immediately if they experience any unusual symptoms, including those of thrombosis listed above. Reserve tofacitinib to treat ulcerative colitis for patients who have failed or do not tolerate tumor necrosis factor (TNF) blockers. Avoid tofacitinib in patients who may have a higher risk of thrombosis. When treating ulcerative colitis, use tofacitinib at the lowest effective dose and limit the use of the 10 mg twice daily dosage to the shortest duration needed.

Question 10:

Regarding Xeljanz and Xeljanz XR, healthcare professionals should:

a. discontinue tofacitinib and promptly evaluate patients with symptoms of thrombosis;
b. reserve tofacitinib to treat ulcerative colitis for patients who have failed or do not tolerate tumor necrosis factor (TNF) blockers;
c. use tofacitinib at the lowest effective dose and limit the use of the 10 mg twice daily dosage to the shortest duration needed;
d. all of the above are recommended by the FDA.

When FDA first approved tofacitinib in 2012, we required a postmarketing clinical trial in patients with RA on background methotrexate, to evaluate the risk of heart-related events, cancer, and infections. The trial is studying two different doses of tofacitinib (5 mg twice daily, which is the currently approved dose for RA, and a higher, 10 mg twice daily dosage) in comparison to a TNF blocker. An interim analysis of the trial's results found an increased occurrence of blood clots and of death in patients treated with tofacitinib 10 mg twice daily compared to patients treated with tofacitinib 5 mg twice daily or a TNF blocker. Based on these results, the 10 mg twice daily treatment was stopped and patients were allowed to continue treatment on 5 mg twice daily.

This safety trial is ongoing. Patients in the 5 mg twice daily group and the TNF blocker group continue to be followed. FDA will reassess these safety issues when the trial has completed and final, verified data are available. We will update the public when additional information is available.

The interim results of the trial, as of January 2019, have identified the following:

- 19 cases of blood clots in the lung out of 3,884 patient-years of follow-up in patients who received tofacitinib 10 mg twice daily, compared to 3 cases out of 3,982 patient-years in patients who received TNF blockers
- 45 cases of death from all causes out of 3,884 patient-years of follow-up in patients who received tofacitinib 10 mg twice daily, compared to 25 cases out of 3,982 patient-years in patients who received TNF blockers

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving tofacitinib or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.[6]

Question 11:

As of January 2019 the FDA identified:

a. 19 cases of blood clots in the lung in patients who received tofacitinib 10mg twice daily, compared to 3 cases in patients who received TNF blockers;
b. 45 cases of death from all causes in patients who received tofacitinib 10mg twice daily, compared to 25 cases in patients who received TNF blockers;
c. neither of the above are true;
d. both of the above are true.

FDA adds Boxed Warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines.[7]

6 855-543-DRUG (3784) and press 4 or druginfo@fda.hhs.gov

[04-30-2019] The Food and Drug Administration (FDA) is advising that rare but serious injuries have happened with certain common prescription insomnia medicines because of sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. These complex sleep behaviors have also resulted in deaths. These behaviors appear to be more common with eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist) than other prescription medicines used for sleep.

As a result, we are requiring a *Boxed Warning*, our most prominent warning, to be added to the prescribing information and the patient Medication Guides for these medicines. We are also requiring a *Contraindication*, our strongest warning, to avoid use in patients who have previously experienced an episode of complex sleep behavior with eszopiclone, zaleplon, and zolpidem.

Serious injuries and death from complex sleep behaviors have occurred in patients with and without a history of such behaviors, even at the lowest recommended doses, and the behaviors can occur after just one dose. These behaviors can occur after taking these medicines with or without alcohol or other central nervous system depressants that may be sedating such as tranquilizers, opioids, and anti-anxiety medicines.

Eszopiclone, zaleplon, and zolpidem are medicines used to treat insomnia in adults who have difficulty falling asleep or staying asleep. They are in a class of medicines called sedative-hypnotics and have been approved and on the market for many years. These insomnia medicines work by slowing activity in the brain to allow sleep. Quality sleep can have a positive impact on physical and mental health.

7 https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia

Health care professionals should not prescribe eszopiclone, zaleplon, or zolpidem to patients who have previously experienced complex sleep behaviors after taking any of these medicines. Advise all patients that

Question 12:

The FDA identified rare but serious injuries because of complex sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake that are more common with:

a. eszopiclone (Lunesta);
b. zaleplon (Sonata);
c. zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist);
d. all of the above.

Question 13:

The FDA issued its strongest warning, a Contraindication, to avoid use of certain insomnia medicines in patients who have previously experienced an episode of complex sleep behavior.

a. True;
b. False.

Question 14:

Concerning these insomnia medicines, the complex sleep behaviors that have caused serious injuries and death occurred:

a. in patients with no history of such behaviors;
b. even at the lowest recommended doses;
c. after just one dose;
d. all of the above.

although rare, the behaviors caused by these medicines have led to serious injuries or death. Tell the patient to discontinue taking these medicines if they experience an episode of complex sleep behavior.

Patients should stop taking your insomnia medicine and contact your health care professional right away if you experience a complex sleep behavior where you engage in activities while you are not fully awake or if you do not remember activities you have done while taking the medicine.

We identified 66 cases of complex sleep behaviors occurring with these medicines over the past 26 years that resulted in serious injuries, including death. This number includes only reports submitted to FDA or those found in the medical literature, so there may be additional cases about which we are unaware. These cases included accidental overdoses, falls, burns, near drowning, exposure to extreme cold temperatures leading to loss of limb, carbon monoxide poisoning, drowning, hypothermia, motor vehicle collisions with the patient driving, and self-injuries such as gunshot wounds and apparent suicide attempts. Patients usually did not remember these events. The underlying mechanisms by which these insomnia medicines cause complex sleep behaviors are not completely understood.

FDA is also reminding the public that all medicines taken for insomnia can impair driving and activities that require alertness the morning after use. Drowsiness is already listed as a common side effect in the drug labels of all insomnia medicines, along with warnings that patients may still feel drowsy the day after taking these products. Patients who take insomnia medicines can experience decreased mental alertness the morning after use even if they feel fully awake.

We communicated safety information associated with certain insomnia medicines in January 2013 (risk of next-morning impairment with zolpidem), May 2013 (approved lower recommended doses for zolpidem), and May 2014 (risk of next-morning impairment with eszopiclone; lowered recommended dose). We are continuing to monitor the safety of insomnia medicines and will update the public as new information becomes available.

To help FDA better track safety issues with medicines, we urge health care professionals and patients to report side effects involving eszopiclone, zaleplon, and zolpidem or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering[8]

[4-9-2019] The U.S. Food and Drug Administration (FDA) has received reports of serious harm in patients who are physically dependent on opioid pain medicines suddenly having these medicines discontinued or the dose rapidly decreased. These include serious withdrawal symptoms, uncontrolled pain, psychological distress, and suicide.

While we continue to track this safety concern as part of our ongoing monitoring of risks associated with opioid pain medicines, we are

Question 15:

The FDA has required changes to prescribing information for opioid medicines:

a. because of reports of serious harm in patients who are physically dependent on opioids suddenly having these medicines discontinued or the dose rapidly decreased;
b. that are intended for use in the inpatient setting;
c. that are intended for use in detoxification programs;
d. all of the above are true.

requiring changes to the prescribing information for these medicines that

8 https://www.fda.gov/drugs/drug-safety-and-availability/fda-identifies-harm-reported-sudden-discontinuation-opioid-pain-medicines-and-requires-label-changes

are intended for use in the outpatient setting. These changes will provide expanded guidance to health care professionals on how to safely decrease the dose in patients who are physically dependent on opioid pain medicines when the dose is to be decreased or discontinued.

Rapid discontinuation can result in uncontrolled pain or withdrawal symptoms. In turn, these symptoms can lead patients to seek other sources of opioid pain medicines, which may be confused with drug-seeking for abuse. Patients may attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin, and other substances.

Opioids are a class of powerful prescription medicines that are used to manage pain when other treatments and medicines cannot be taken or are not able to provide enough pain relief. They have serious risks, including abuse, addiction, overdose, and death. Examples of common opioids include codeine, fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, and oxymorphone.

Health care professionals should not abruptly discontinue opioids in a patient who is physically dependent. When you and your patient have agreed to taper the dose of opioid analgesic, consider a variety of factors, including the dose of the drug, the duration of treatment, the type of pain being treated, and the physical and psychological attributes of the patient. No standard opioid tapering schedule exists that is suitable for all patients. Create a patient-specific plan to gradually taper the dose of the

Question 16:

For opioid dependent patients, healthcare professionals should:

a. abruptly discontinue opioids in a patient who is physically dependent to immediately decrease risk of harm;
b. use the standard opioid tapering schedule;
c. consider dose, duration, type of pain, and attributes of the patient when agreeing with the patient to taper the dose;
d. taper the patient from opioids regardless of whether the patient has secured any ongoing monitoring and support.

opioid and ensure ongoing monitoring and support, as needed, to avoid serious withdrawal symptoms, worsening of the patient's pain, or psychological distress (For tapering and additional recommendations, see Additional Information for Health Care Professionals).

Additional Information for Health Care Professionals

- There are no standard opioid tapering schedules that are suitable for all patients. A patient-specific plan should be used to taper the dose of the opioid gradually.

- In general, for patients who are physically dependent on opioids, taper by an increment of no more than 10 percent to 25 percent every 2 to 4 weeks. It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper.

- If the patient is experiencing increased pain or serious withdrawal symptoms, it may be necessary to pause the taper for a period of time, raise the opioid analgesic to the previous dose, and then once stable, proceed with a more gradual taper.

- When managing patients taking opioid analgesics, particularly those who have been treated for a long duration and/or with high doses for chronic pain, ensure that a multimodal approach to pain management,

Question 17:

For opioid dependent patients, healthcare professionals should consider:

a. a taper by an increment of no more than 10-25% every 2-4 weeks;
b. abandoning the opioid taper, if the patient is experiencing increased pain or serious withdrawal symptoms;
c. increasing the opioid dose above the previous dose;
d. reporting all patients to their state pharmacy board.

including mental health support (if needed), is in place prior to initiating an opioid analgesic taper. A multimodal approach to pain management may optimize the treatment of chronic pain, as well as assist with the successful tapering of the opioid analgesic.

- Patients who have been taking opioids for shorter time periods may tolerate a more rapid taper.

- When opioid analgesics are being discontinued due to a suspected substance use disorder, evaluate and treat the patient, or refer him/her for evaluation and treatment of the substance use disorder. Treatment should include evidence-based approaches such as medication assisted treatment of opioid use disorder. Complex patients with comorbid pain and substance use disorders may benefit from referral to a specialist.

- Frequent follow-up with patients is important. Reassess the patient regularly to manage pain and withdrawal symptoms that emerge. Common withdrawal symptoms include:
  - Restlessness
  - Rhinorrhea
  - Perspiration
  - Lacrimation
  - Yawning
  - Chills and myalgia

- Other symptoms also may develop, including:
  - Irritability
  - Insomnia
  - Joint pain
  - Abdominal cramps
  - Nausea and vomiting
  - Anxiety
  - Backache
  - Weakness
  - Anorexia
  - Diarrhea
  - Increased blood pressure or heart rate
  - Increased breathing rate

- Patients should also be monitored for suicidal thoughts, use of other substances, or any changes in mood.

Question 18:

For opioid tapering patients, the FDA recommends frequent follow-up with patients to regularly manage pain and withdrawal symptoms such as:

a. runny nose and restlessness;
b. anxiety and increased breathing rate;
c. diarrhea;
d. all of the above.

FDA adds Boxed Warning for increased risk of death with gout medicine Uloric (febuxostat)[9]

[2-21-2019] The U.S. Food and Drug Administration (FDA) has concluded there is an increased risk of death with Uloric (febuxostat) compared to another gout medicine, allopurinol. This conclusion is based on our in-depth review of results from a safety clinical trial that found an increased risk of heart-related death and death from all causes with Uloric.
As a result, we are updating the Uloric prescribing information to require a *Boxed Warning*, our most prominent warning, and a new patient Medication Guide. We are also limiting the approved use of Uloric to certain patients who are not treated effectively or experience severe side effects with allopurinol.

Uloric was FDA-approved in 2009 to treat a type of arthritis called gout in adults. Gout happens when a naturally occurring substance in the body called uric acid builds up and causes sudden attacks of redness, swelling, and pain in one or more joints. Uloric works by lowering uric acid levels in the blood. Gout is a chronic disease that affects approximately 8.3 million adults in the U.S.[1] The number of medicines to treat gout is limited and there is an unmet need for treatments for this disease.

9 https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-increased-risk-death-gout-medicine-uloric-febuxostat

Patients should tell your health care professional if you have a history of heart problems or stroke and discuss the benefits and risks of using Uloric to treat your gout. Seek emergency medical attention right away if you experience the following symptoms while taking Uloric:

- Chest pain
- Shortness of breath
- Rapid or irregular heartbeat
- Numbness or weakness on one side of your body
- Dizziness
- Trouble talking
- Sudden severe headache
-

Do not stop taking Uloric without first talking to your health care professional, as doing so can worsen your gout.

Question 19:

Uloric (febuxostat):

a. is used to treat a type of arthritis called gout in adults;
b. works by lowering uric acid levels in the blood;
c. has an increased risk of death when compared to allopurinol;
d. all of the above are true.

Health care professionals should reserve Uloric for use only in patients who have failed or do not tolerate allopurinol. Counsel patients about the cardiovascular risk with Uloric and advise them to seek medical attention immediately if they experience the symptoms listed above.

When we approved Uloric in 2009, we included a *Warning and Precaution* regarding possible cardiovascular events in patients treated with Uloric in the current prescribing information and required the drug

manufacturer, Takeda Pharmaceuticals, to conduct a large postmarket safety clinical trial. The trial was conducted in more than 6,000 patients with gout treated with either Uloric or allopurinol. The primary outcome was a combination of heart-related death, non-deadly heart attack, non-deadly stroke, and a condition of inadequate blood supply to the heart requiring intervention, called unstable angina.

The results showed that overall, Uloric did not increase the risk of these combined events compared to allopurinol. However, when the outcomes were evaluated separately, Uloric showed an increased risk of heart-related deaths and death from all causes. In patients treated with Uloric, 15 deaths from heart-related causes were observed for every 1,000 patients treated for a year compared to 11 deaths from heart-related causes per 1,000 patients treated with allopurinol for a year. In addition, there were 26 deaths from any cause per 1,000 patients treated for a year with Uloric compared to 22 deaths per 1,000 patients treated for a year with allopurinol.

This safety trial was also discussed at a public Advisory Committee meeting of outside experts on January 11, 2019.

Question 20:

Regarding Uloric (febuxostat) health care professionals should:

a. use only in patients who have failed or do not tolerate allopurinol;
b. counsel patients about the cardiovascular risk with Uloric;
c. counsel patients to seek emergency medical attention if they experience a sudden severe headache or have trouble talking;
d. all of the above.

FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR)[10]

[12-19-2019] The U.S. Food and Drug Administration (FDA) is warning that serious breathing difficulties may occur in patients using gabapentin (Neurontin, Gralise, Horizant) or pregabalin (Lyrica, Lyrica CR) who have respiratory risk factors. These include the use of opioid pain medicines and other drugs that depress the central nervous system, and conditions such as chronic obstructive pulmonary disease (COPD) that reduce lung function. The elderly are also at higher risk.

Gabapentin and pregabalin are FDA-approved for a variety of conditions, including seizures, nerve pain, and restless legs syndrome.

FDA's evaluation shows that the use of these medicines, often referred to as gabapentinoids, has been growing for prescribed medical use, as well as misuse and abuse. Gabapentinoids are often being combined with CNS depressants, which increases the risk of respiratory depression. CNS depressants include opioids, anti-anxiety medicines, antidepressants, and antihistamines. There is less evidence supporting the risk of serious breathing difficulties in healthy individuals taking gabapentinoids alone. We will continue to monitor these medicines as part of our routine monitoring of all FDA-approved drugs.

We are requiring new warnings about the risk of respiratory depression to be added to the prescribing information of the gabapentinoids. We have also required the drug manufacturers to conduct clinical trials to further evaluate their abuse potential, particularly in combination with opioids, because misuse and abuse of these products together is increasing, and co-use may increase the risk of respiratory depression. Special attention will be paid to the respiratory depressant effects during this abuse potential evaluation.

Healthcare professionals should know:

10 https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-serious-breathing-problems-seizure-and-nerve-pain-medicines-gabapentin-neurontin

• FDA is warning that serious, life-threatening, and fatal respiratory depression has been reported with the gabapentinoids, gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR). Most cases occurred in association with co-administered central nervous system (CNS) depressants, especially opioids, in the setting of underlying respiratory impairment, or in the elderly.

• FDA's evaluation of respiratory depression with the gabapentinoids provides some evidence contrary to the widely held belief that gabapentinoids lack drug interactions and have wide therapeutic indices. Published studies demonstrate these drugs can behave in an additive way to potentiate central nervous system (CNS) and respiratory depression.

• When co-prescribing gabapentinoids with another CNS depressant, particularly an opioid, or in patients with underlying respiratory impairment, initiate the gabapentinoid at the lowest dose.

• Adjust the dose of both gabapentin and pregabalin in patients with renal impairment and patients undergoing hemodialysis, because both drugs are excreted by the kidneys.

• Monitor for symptoms of respiratory depression and sedation, especially when co-prescribing gabapentinoids with an opioid or other CNS depressant such as a benzodiazepine or when prescribing to patients with underlying respiratory impairment, or elderly patients.

Question 21:

The FDA warns that serious breathing difficulties may occur in patients using gabapentin or pregabalin who have certain risk factors. The risk factors include:

a. use of opioid pain medicines;
b. chronic obstructive lung disease (COPD);
c. being elderly;
d. all of the above.

Question 22:

The FDA's evaluation of gabapentinoids provides some evidence contrary to the widely held belief that gabapentinoids:

a. lack drug interactions;
b. have wide therapeutic indices;
c. both of the above;
d. none of the above.

Return this ANSWER SHEET with the $20.00 Program Fee payable to:

Select CE, P.O. Box 21186, Columbus, Ohio 43221-0186

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ANSWERS: FDA Drug Safety Communications – 2020

ACPE Program Number: 0487-0000-19-003-H05-P
(Expiration Date: January 11, 2023)

Circle the answer for each question (questions are imbedded in the program).

1.	a	b	c	d	12.	a	b	c	d
2.	a	b	c	d	13.	a	b		
3.	a	b	c	d	14.	a	b	c	d
4.	a	b	c	d	15.	a	b	c	d
5.	a	b	c	d	16.	a	b	c	d
6.	a	b	c	d	17.	a	b	c	d
7.	a	b	c	d	18.	a	b	c	d
8.	a	b	c	d	19.	a	b	c	d
9.	a	b	c	d	20.	a	b	c	d
10.	a	b	c	d	21.	a	b	c	d
11.	a	b	c	d	22.	a	b	c	d

23. After completing this CE activity, I am able to list 7 rare but serious events, and their associated drugs, for which the FDA issued Drug Safety Communications: Yes No

24. I am a pharmacist: Yes No

25. I am a nurse: Yes No

26. I am another type of healthcare professional: Yes No

27. This CE activity met my educational needs: Yes No

28. The learning material was useful: Yes No

29. The teaching and learning methods (e.g., format; questions embedded in the program) fostered active learning and were effective: Yes No

30. The learning assessment (the post-test) was appropriate: Yes No

31. The test questions were relevant to the goals of the CE activity: Yes No

32. The test questions were at an appropriate level of difficulty: Yes No

33. The CE activity was presented in a fair and unbiased manner: Yes No

34. If you perceived any bias or commercialism, please describe: