continuing education for pharmacists

Volume XXXIII, No. 10

New Drugs: Lynparza, Opdivo, Rapivab, and Savaysa

Thomas A. Gossel, R.Ph., Ph.D., Professor Emeritus, Ohio Northern University, Ada, Ohio

Dr. Thomas A. Gossel has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide information on edoxaban (Savaysa™), nivolumab (Opdivo®), olaparib (Lynparza™) and peramivir (Rapivab™).

Objectives. At the completion of this activity, the participant will be able to:

1. recognize signs and symptoms, and key features of targeted pathologies for these new drugs, including information on their prevalence in the population;
2. select the indication(s), pharmacologic action(s) and clinical applications for each drug;
3. recognize important therapeutic uses for the drugs and their applications in specified pathologies; and
4. demonstrate an understanding of adverse effects and toxicity, significant drug-drug interactions, and patient counseling information for these drugs.

The four new-molecular entity drugs discussed in this lesson are approved to treat a wide variety of pathologies (Table 1). This lesson provides a brief introduction to the therapeutic agents, and neither depth nor expanse is intended to extend beyond an overview of the topic. The reader is, therefore, encouraged to consult the products' full Prescribing Information leaflet (package insert), FDA-approved *Medication Guide* when available, and other published sources and websites for detailed descriptions.

Edoxaban (Savaysa)

Discovered in 1945 for use as an agricultural rodenticide, warfarin soon became widely accepted in human medicine for stroke prophylaxis in atrial fibrillation (AF) and anticoagulant use in venous thromboembolism (VTE). Although extremely effective in these applications, the drug posed significant disadvantages with its use. These disadvantages, discussed subsequently, have been the basis for development of newer agents. Edoxaban is the latest entry into this novel class of therapeutic agents that offer protection against stroke in AF and thromboembolic events.

Indications and Use. Savaysa (sa-VAYÉ-sah) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF. It is also indicated for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following five to 10 days of initial therapy with a parenteral anticoagulant.

Anticoagulants in atrial fibrillation and venous thromboembolism. AF is one of the most common types of abnormal cardiac rhythm. When the heart's atria do not contract properly, this allows thrombi to form, which can dislodge and migrate to the brain or other parts of the body. VTE includes DVT and PE. DVT is a thrombus that forms in a vein deep in the body, usually in the lower leg or thigh. PE is a potentially fatal condition that results when a thrombus within a deep vein dislodges (i.e., becomes an embolus) and circulates to an artery in the lungs and blocks blood flow. The number of patients with AF is estimated at approximately 6 million in the United States and is projected to at least double by 2050. VTE is a very common condition, with an estimated 900,000 incidents or recurrent events in the United States each year.

Until 2009, vitamin K antagonists, including warfarin, were the only class of oral anticoagulants available to confer prophylaxis against stroke in AF. Although these drugs are highly effective in prevention of thromboembolism, their use is limited in clinical practice. Limitations of warfarin include a slow onset of action; inadequate anticoagulation; the need for frequent, complex, dose adjustments; increased risk of bleeding, particularly in the elderly; variability in dose response; drug and food interactions; and lack of laboratory standardization in coagulation monitoring. The drug also has a narrow therapeutic index that necessitates frequent monitoring and dose adjustments resulting in substantial risk and patient inconvenience. This limitation, in turn, translates into poor patient adherence and probably contributes to

Table 1
Selected new drugs

Generic (Trade Name)	Distributor	Indication	Dose*	Dosage Form	Most Common Side Effects	Medication Guide[±]
Edoxaban (Savaysa)	Daiichi Sankyo	stroke reduction in atrial fib; DVT, and pulmonary embolism	60 mg PO once daily	15, 30, 60 mg tablets	(≥1%): bleeding, rash, abnormal liver function tests, anemia	Yes
Nivolumab (Opdivo)	Bristol-Myers Squibb	unresectable or metastatic melanoma; metastatic squamous NSCLC[δ]	3 mg/kg IV over 60 min every 2 weeks	single-use vials for IV infusion, 40mg/4mL 100mg/10mL	(≥20%): rash, fatigue, cough, dyspnea, musculoskeletal pain, decreased appetite, nausea, constipation	Yes
Olaparib (Lynparza)	AstraZeneca	advanced ovarian cancer	400 mg PO twice daily	50 mg capsules	(≥20%): anemia, nausea, fatigue, vomiting, diarrhea, dysgeusia, dyspepsia, headache, decreased appetite, nasopharyngitis, pharyngitis, URI, cough, arthralgia, musculoskeletal pain, myalgia, back pain, dermatitis, abdominal pain/discomfort, rash	Yes
Peramivir (Rapivab)	BioCryst	acute uncomplicated influenza	600 mg IV over a minimum of 15 min	single-use vials for IV infusion 200mg/20mL	(≥2%): diarrhea	No

*Recommended dose for most patients [±]Availability at the time of publication of this lesson [δ]non-small cell lung cancer

the systematic underuse of vitamin K antagonists for stroke prevention.

A new class of oral anticoagulants is now available that inhibits thrombin or activated factor X (FXa) in a dose-dependent manner and, therefore, offers potential advantages over vitamin K antagonists. Their advantages include rapid onset and offset of action, absence of an effect of dietary vitamin K intake on their activity, fewer drug interactions, and less chance for intracranial bleeding compared to warfarin. Their predictable anticoagulant effects enable administration of fixed doses without the need for routine coagulation monitoring, thereby simplifying treatment and thus, improved patient adherence. The new oral anticoagulants are at least as safe and effective as warfarin for prevention of stroke and systemic embolism in patients with AF. The newer drugs fall into two drug classes: the direct thrombin inhibitors (dabigatran/Pradaxa) and the oral FXa inhibitors (rivaroxaban/Xarelto, apixaban/Eliquis, and edoxaban/Savaysa).

Mechanism of Action. Edoxaban is a selective inhibitor of FXa, a key enzyme located at the confluence of the intrinsic and extrinsic coagulation pathways. Edoxaban inhibits free FXa within the prothrombinase complex and inhibits thrombin-induced platelet aggregation. Inhibition of FXa in the coagulation cascade reduces thrombin generation, thereby reducing thrombus formation. As a result of FXa inhibition, edoxaban prolongs clotting time tests such as prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). Changes observed in PT, INR, and aPTT at the expected therapeutic dose, however, are small, subject to a high degree of variability and not useful in monitoring the anticoagulant effect of edoxaban.

Efficacy and Safety. Safety and efficacy in treating patients with AF not caused by cardiac valve disease was studied in a clinical trial of 21,105 participants. The trial compared 30 and 60 mg doses of Savaysa with warfarin for their effects on rates of stroke and dangerous systemic emboli. The trial results showed the higher dose of Savaysa to be similar to warfarin for reduction in the risk of stroke. While warfarin is highly effective in reducing the risk of stroke in patients with AF, it increases the risk of bleeding. Savaysa demonstrated significantly less major bleeding compared to warfarin.

Savaysa for treatment of patients with DVT and PE was studied in 8,292 participants. The study compared safety and efficacy

of the drug to warfarin for treating patients with a DVT and/or PE to reduce the rate of recurrence of symptomatic VTE events. In the trial, 3.2 percent of participants taking Savaysa had a symptomatic recurrent VTE compared to 3.5 percent of those taking warfarin.

Savaysa has a *Boxed Warning* that advises the drug is less effective in nonvalvular AF patients with a creatinine clearance (CrCL) greater than 95 mL/min. Such patients have an increased risk of ischemic stroke compared to similar patients given warfarin. As with other anticoagulants, the *Boxed Warning* counsels that premature discontinuation of Savaysa increases the risk of ischemic events and notes that spinal or epidural hematomas may occur in persons treated with Savaysa who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis.

Warnings and Precautions. The following **warnings** and **precautions** are listed:

•*Serious and potentially fatal bleeding*: Promptly evaluate signs and symptoms of blood loss.

•*Mechanical heart valves or moderate to severe mitral stenosis*: Use is not recommended.

Contraindications. Active pathological bleeding is a **contraindication** to the drug's use.

Drug Interactions. Co-administration of anticoagulants, antiplatelet drugs, and thrombolytics may increase the risk of bleeding. Long-term concomitant treatment with edoxaban and other anticoagulants is not recommended. Short-term co-administration may be needed for patients transitioning to or from edoxaban. Carefully monitor for bleeding in patients who require chronic treatment with low-dose aspirin and/or other NSAIDs.

Avoid concomitant use with the P-glycoprotein (P-gp) *inducer* rifampin. No dose reduction is recommended for concomitant P-gp *inhibitor* use in patients with AF.

Administration, Dosing, and Availability. Savaysa may be taken without regard to food. If a dose is missed, the dose should be taken as soon as possible on the same day. Dosing should resume the next day according to the normal dosing schedule. The dose should not be doubled to make up for a missed dose.

For nonvalvular AF, the recommended dose is 60 mg once daily in patients with CrCL >50 to ≤95 mL/min. Edoxaban should not be initiated in patients with CrCL >95 mL/min. For treatment of DVT and PE the recommended dose is 60 mg once daily. The recommended dose is 30 mg once daily for patients with CrCL 15 to 50 mL/min, body weight ≤60 kg, or for those who use certain P-gp inhibitors.

Savaysa is available in 15 mg, 30 mg, and 60 mg tablets.

Patient Counseling. An FDA-approved *Medication Guide* must be dispensed with each new or refill prescription for Savaysa. Specific points for counseling are summarized in Table 2.

Nivolumab (Opdivo)

Opdivo (op-DEE-voh) is the seventh new melanoma drug approved since 2011. Others include ipilimumab (2011), peginterferon alfa-2b (2011), vemurafenib (2011), dabrafenib (2013), trametinib (2013) and pembrolizumab (2014).

Opdivo was approved under FDA's accelerated approval program, which allows approval of a drug to treat a serious or life-threatening disease based on clinical data showing the drug has an effect on a surrogate endpoint reasonably likely to predict clinical benefit to patients. This program provides earlier patient access to promising new drugs while the company conducts additional clinical trials to confirm the drug's benefit.

Indications and Use. Opdivo is indicated for treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab (Yervoy) and, if BRAF V600 mutation positive, a BRAF inhibitor. The RAS-RAF-mitogen-activated protein kinase (MAPK) signaling pathway transmits external signals from growth factors and the microenvironment to influence cancer cell growth, differentiation and survival. The BRAF gene encodes the BRAF protein, a critical component of the MAPK pathway. Mutations in BRAF that force "always on" constitutive activity in BRAF are found in about one-half of melanomas.

Table 2
Patient counseling information for Savaysa*

Inform patients:
- to read the FDA-approved *Medication Guide* each time they receive this drug;
- that they may bleed more easily, may bleed longer, or bruise more easily when treated with Savaysa;
- to report any unusual bleeding immediately to their healthcare provider;
- to take Savaysa exactly as prescribed;
- to not discontinue the drug without talking to their physician who prescribed it;
- to inform their healthcare providers that they are taking Savaysa before any surgery, medical, or dental procedure is scheduled;
- to inform their healthcare providers and dentists if they plan to take, or are taking any prescription medications, over-the-counter drugs or herbal products;
- to inform their physician immediately if they become pregnant or intend to become pregnant, or are breastfeeding or intend to breastfeed during treatment with Savaysa;
- that if they are having spinal anesthesia or spinal puncture, patients should watch for signs and symptoms of spinal or epidural hematoma, such as back pain, tingling, numbness (especially in the lower limbs), muscle weakness, and stool or urine incontinence. If any of these symptoms occur, the patient should contact his or her physician immediately.

*A complete list of counseling information is available in the product's *Medication Guide*.

Opdivo was also approved by FDA on March 4, 2015 to treat patients with metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy treatment.

Melanoma. Melanoma forms in the body's melanocyte cells, which develop skin pigment. The cancer is potentially curable when diagnosed early, but historically, the prognosis of patients with metastatic disease has been poor, with median survival of less than one year, and overall five-year mortality close to 90 percent. For almost 40 years before the approval of ipilimumab, no single drug or combination of drugs demonstrated a significant effect on overall survival of patients with metastatic melanoma. Recent research in the fields of tumor biology and immunology, however, has led to development of new targeted and immunotherapeutic agents that prolong progression-free survival and overall survival in patients with advanced melanoma.

At present, melanoma remains the fifth and sixth most common type of cancer in men and women, respectively, in the United States. The American Cancer Society estimates that 73,870 Americans (42,670 men and 31,200 women) will be diagnosed with melanoma, and 9,940 (6,640 men and 3,300 women) will die from the disease in 2015. Although melanoma accounts for less than 4 percent of all dermatologic cancers, it is responsible for 80 percent of all skin cancer deaths.

Mechanism of Action. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with programmed cell death-1 ligand-1 (PD-L1) and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

Efficacy and Safety. Opdivo's efficacy was demonstrated in 120 clinical trial participants with unresectable or metastatic melanoma. Results showed that 32 percent of participants receiving Opdivo experienced tumor shrinkage. This effect lasted for more than six months in approximately one-third of the participants who experienced tumor shrinkage.

Safety was evaluated in the overall trial population of 268 participants treated with Opdivo and 102 participants treated with chemotherapy. The most common adverse effects of the drug were rash, itching, cough, upper respiratory tract infections, and edema. The most serious effects were severe immune-mediated adverse effects involving healthy organs, including the lung, colon, liver, kidneys and hormone-producing glands.*

Warnings and Precautions. The following **warnings** and **precautions** are listed:

• *Immune-mediated adverse reactions*: Withhold treatment and administer corticosteroids based on the severity of the reaction;

• *Immune-mediated pneumonitis*: Withhold for moderate and permanently discontinue for severe or life-threatening pneumonitis;

• *Immune-mediated colitis*: Withhold for moderate or severe and permanently discontinue for life-threatening colitis;

• *Immune-mediated hepatitis*: Monitor for changes in liver function. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation;

• *Immune-mediated nephritis and renal dysfunction*: Monitor for changes in renal function. Withhold for moderate or severe, and permanently discontinue for life-threatening serum creatinine elevation;

• *Immune-mediated hypothyroidism and hyperthyroidism*: Monitor for changes in thyroid function. Initiate thyroid hormone replacement or medical management as needed;

**On Sept. 1, 2015, alerts were issued on new adverse drug reactions. Pharmacists should review current literature for the most up-to-date information.*

Table 3
Patient counseling information for Opdivo*

Inform patients:
• to read the FDA-approved *Medication Guide* each time they receive this drug;
• of the risk of immune-mediated adverse reactions that may require corticosteroid treatment and interruption or discontinuation of Opdivo, including pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, and hypothyroidism and hyperthyroidism. Advise them to contact their physician immediately for any new or worsening sign or symptom suggesting these problems;
• of the importance of keeping scheduled appointments for blood work or other laboratory tests;
• (females): of reproductive potential of the potential risk to a fetus and to inform their physician of a known or suspected pregnancy;
• (females): of reproductive potential to use effective contraception during treatment with Opdivo and for at least five months following the last dose of the drug;
• (females): not to breastfeed while taking Opdivo.

*A complete list of counseling information is available in the product's *Medication Guide*.

• *Embryofetal toxicity*: Opdivo can cause fetal harm. Advise patient of potential risk to a fetus and use of effective contraception during treatment and for at least five months after the last dose.

Contraindications. There are no **contraindications** listed.

Drug Interactions. No formal pharmacokinetic drug-drug interaction studies have been conducted with Opdivo.

Administration, Dosing, and Availability. The recommended dose is 3 mg/kg administered as an intravenous infusion over 60 minutes every two weeks, until disease progression or unacceptable toxicity.

Opdivo is available in single-use vials containing 40 mg/4 mL and 100 mg/10 mL. Vials should neither be shaken nor frozen.

Patient Counseling. An FDA-approved *Medication Guide* must be dispensed each time the patient receives Opdivo. Specific points for counseling are summarized in Table 3.

Olaparib (Lynparza)

FDA approved Lynparza (lin-PAR-zah), along with a genetic test called BRACAnalysis CDx, a companion diagnostic that will detect the presence of mutations in the BRCA genes (gBRCAm) in blood. The BRCA genes are involved with repairing damaged DNA and normally work to suppress tumor growth. Women with mutations resulting in defective BRCA genes are more likely to develop ovarian cancer, and it is estimated that 10 to 15 percent of all ovarian cancer is associated with these hereditary BRCA mutations.

Indications and Use. Lynparza is indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. As with Opdivo, Lynparza was approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Ovarian Cancer. Every year approximately 225,000 women worldwide develop epithelial ovarian cancer. It is the fourth most common cause of female cancer death in the developed world. The American Cancer Society estimates that 21,000 women in the United States will develop the disease in 2015, which will contribute to 14,180 deaths. The age-standardized incidence of the disease has been reported at 9.4 per 100,000 population in more developed countries, and five per 100,000 population elsewhere. The median age of patients enrolled in most randomized trials is 58 years, several years younger than the median age at diagnosis (63 years) in the overall population. Women with a genetic predisposition for ovarian cancer are diagnosed roughly 10 years earlier than the median age of diagnosis overall.

The reason for the high death rate is late presentation in most cases, i.e., the disease is widely metastatic at the time of diagnosis. Although with modern management, a significant proportion of women attain complete response, most who present with advanced disease will develop recurrence within 18 months. For some patients, the tumor remains sensitive to periodic retreatment with platinum-based chemotherapy, becoming relatively chronic and free of debilitating symptoms until chemoresistance restricts further treatment options.

The management of epithelial ovarian cancer requires expertise in surgery, use of chemotherapy and newer drugs, imaging, histopathology, and palliation (relieving symptoms without actually curing the disease); specialist multidisciplinary teamwork is, therefore, essential to achieve optimum outcomes. The histopathology of ovarian tumors is heterogeneous and each ovarian cancer subtype harbors genetic mutations that are being assessed for their potential to predict the efficacy of molecularly targeted treatments. With an overall five-year survival following diagnosis of roughly 40 percent, along with the continuing development of new treatments, the medium-term outlook for women with ovarian cancer is far better than it was formerly. However, at present, the majority of patients will still die from the disease.

Mechanism of Action. Olaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and repair of DNA single-strand breaks.

Efficacy and Safety. Lynparza's efficacy was examined in a study where 137 participants with gBRCAm-associated ovarian cancer received the drug. The study was designed to measure objective response rate (ORR), or the percentage of participants who experienced partial shrinkage or complete disappearance of the tumor. Results showed 34 percent of participants experienced ORR for an average of 7.9 months.

Common adverse effects included nausea, fatigue, vomiting, diarrhea, distorted taste (dysgeusia), indigestion, headache, decreased appetite, common cold-like symptoms (nasopharyngitis), cough, joint pain, musculoskeletal pain, muscle pain, back pain, abdominal pain, and rash. Serious adverse effects included development of myelodysplastic syndrome, a condition where bone marrow is unable to produce sufficient functioning blood cells; acute myeloid leukemia, a bone marrow cancer; and lung inflammation.

Warnings and Precautions. The following **warnings** and **precautions** are listed:

- *Myelodysplastic syndrome/ Acute Myeloid Leukemia (MDS/ AML)*: Some cases have been fatal. Monitor patients for hematological toxicity at baseline and monthly thereafter. Discontinue if MDS/ AML is confirmed;
- *Pneumonitis*: This occurred in patients exposed to Lynparza, and some cases were fatal. Interrupt treatment if pneumonitis is suspected. Discontinue if pneumonitis is confirmed;
- *Embryo-Fetal toxicity*: Lynparza can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to avoid pregnancy.

Contraindications. No **contraindications** are listed.

Drug Interactions. Olaparib is metabolized primarily by CYP3A. Strong CYP3A *inhibitors* (e.g., itraconazole, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, posaconazole, ritinovir, lopinavir/ritonavir, indinavir, saquinavir, nelfinavir,

Table 4
Patient counseling information for Lynparza*

Inform patients:
- to read the FDA-approved *Medication Guide* each time they receive this drug;
- to contact their physician if they experience weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, blood in urine or stool, and/or laboratory findings of low blood cell counts, or a need for blood transfusions. This may be a sign of hematological toxicity or a more serious uncommon bone marrow problem called "myelodysplastic syndrome" (MDS) or "acute myeloid leukemia" (AML), which have been reported in patients treated with Lynparza;
- to contact their physician if they experience any new or worsening respiratory symptoms including shortness of breath, fever, cough, or wheezing;
- that mild or moderate nausea and/or vomiting is very common in patients receiving Lynparza and that they should contact their physician who will advise on available antiemetic treatment options;
- (females): of reproductive potential of the potential risk to a fetus and to inform their physician of a known or suspected pregnancy;
- (females): of reproductive potential to use effective contraception during treatment and for at least one month after receiving the last dose of Lynparza;
- (females): not to breastfeed while taking Lynparza.

*A complete list of counseling information is available in the product's *Medication Guide*.

boceprevir, telaprevir) and moderate CYP3A *inhibitors* (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil) should be avoided concomitantly with Lynparza. The manufacturer recommends that if strong or moderate inhibitors must be co-administered, the dose of Lynparza should be reduced. Grapefruit and Seville oranges should be avoided during Lynparza therapy

The use of strong CYP3A *inducers* (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) and moderate CYP3A4 *inducers* (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided concomitantly with Lynparza. If a moderate CYP3A inducer cannot be avoided, be aware of a potential for decreased efficacy of Lynparza.

Clinical studies of Lynparza in combination with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

Administration, Dosing, and Availability. The recommended dose is 400 mg taken twice daily for a total daily dose of 800 mg. Continue treatment until disease progression or unacceptable toxicity. Instruct patients who miss a dose of Lynparza to take their next dose at its scheduled time. Capsules should be swallowed whole. Capsules that appear deformed or show evidence of leakage should not be taken.

Lynparza is available in 50 mg capsules.

Patient Counseling. An FDA-approved *Medication Guide* must be dispensed with each new or refill prescription for Lynparza. Specific points for counseling are summarized in Table 4.

Peramivir (Rapivab)

Rapivab (RAP-i-vab) is the third neuraminidase inhibitor approved by FDA to treat flu infection, and the first approved as an IV formulation. Other neuraminidase inhibitors to treat flu include oseltamivir (Tamiflu), administered orally, and zanamivir (Relenza), which is inhaled. Prior to Rapivab's approval, treatment options for hospitalized patients, therefore, were limited to oral or inhaled products. Older antiviral drugs for influenza, amantadine (Symmetrel) and rimantadine (Flumadine), are no longer recommended by the U.S. Centers for Disease Control and Prevention (CDC) because of a high level of resistance to them, and they are not effective against influenza B.

Indications and Use. Rapivab is indicated for treatment of acute uncomplicated influenza in patients 18 years and older who have been symptomatic for no more than two days. Efficacy was based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were also enrolled.

Influenza. Influenza is a highly contagious and virulent respiratory illness caused by influenza viruses. The Spanish influenza pandemic (pandemic: characterized by being widespread across cultures, even worldwide) from 1918 to 1920 is estimated to have infected about half of the world's population and to have resulted in 40 to 50 million deaths. Later pandemics of the twentieth century have each claimed as many as one million deaths. Although mortality has been substantially lower in more recent pandemics and in seasonal epidemics compared with the 1918 pandemic, economic costs have been extremely high.

Influenza viruses are single-strand RNA viruses belonging to the Orthomyxoviridae family. They are classified into three types: A, B, and C, based on antigenic differences in their nucleoprotein and matrix proteins. Influenza C is the least common and usually causes only mild disease in children. It does not cause epidemics or pandemics, and has not been a focus of either drug or vaccine development. Influenza B can cause large epidemics, but not pandemics. Influenza A, the most important of the viruses, may cause pandemics and is associated with significant seasonal morbidity and mortality.

The virus enters cells of the host's respiratory tract and, if not neutralized by antibodies, begins proliferating. Systemic symptoms, such as fever, myalgia, headache, malaise, rhinitis, sore throat, and cough, are believed to result from the release of inflammatory mediators in response to viral activity.

The incubation period is 18 to 72 hours, but viral shedding may occur up to 24 hours before symptom onset and continue for five to 10 days. Influenza is typically uncomplicated and self-limiting in otherwise healthy patients. However, severe complications such as pneumonia, encephalitis, respiratory failure, and multiorgan failure can occur and, as noted above, lead to death. According to estimates from the World Health Organization, three to five million cases of severe influenza-related illness and 250,000 to 500,000 influenza-related deaths occur worldwide every year. The CDC estimates that 5 to 20 percent of the American population suffers from influenza and more than 200,000 people are hospitalized from seasonal flu-related complications each year.

Peramivir and other antiviral drugs used to treat influenza are not substitutes for early, annual flu vaccination. The American Academy of Pediatrics recommends annual seasonal influenza immunization for all persons six months of age and older, including children and adolescents.

Mechanism of Action. Peramivir is an inhibitor of influenza virus neuraminidase, an enzyme that releases viral particles from the plasma membrane of infected cells.

Efficacy and Safety. Efficacy was established in 297 participants with confirmed influenza who were randomly assigned to receive Rapivab 300 mg or 600 mg, or placebo. Overall, participants receiving Rapivab 600 mg had combined influenza symptoms alleviated 21 hours sooner, on average, than those receiving placebo, which is consistent with other drugs in the same class. Those receiving Rapivab 600 mg also recovered to normal temperature approximately 12 hours sooner, compared to placebo.

Common adverse effects observed in Rapivab-treated participants included diarrhea. Rare but serious adverse effects included skin or hypersensitivity reactions and neuropsychiatric events.

Warnings and Precautions. The following **warnings** and **precautions** are listed:

• *Serious skin/hypersensitivity reactions:* Reactions such as Stevens-Johnson syndrome and erythema multiforme have been reported. Appropriate treatment should be instituted if a serious skin reaction occurs or is suspected;

• *Neuropsychiatric events*: Patients with influenza may be at an increased risk of hallucinations, delirium and abnormal behavior early in their illness, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy, but can occur in uncomplicated influenza as well. Monitor for signs of abnormal behavior.

Contraindications. No **contraindications** are listed.

Drug Interactions. Inactivated influenza vaccine can be administered at any time relative to use of Rapivab. For live attenuated influenza vaccine (LAIV), antiviral drugs may inhibit viral replication and, thus, may reduce vaccine efficacy. Because of the potential for interference between Rapivab and LAIV, avoid use of LAIV within two weeks before or 48 hours after administration of Rapivab unless medically indicated.

The potential for CYP-mediated interactions involving Rapivab with other drugs is low, based on the known elimination pathway of Rapivab, and data from *in vitro* studies indicating Rapivab neither induces nor inhibits cytochrome P450 enzymes.

Administration, Dosing, and Availability. Rapivab is administered as a single dose within two days of onset of influenza symptoms. The recommended dose is 600 mg, administered by intravenous infusion over 15 to 30 minutes. Significantly increased drug exposures were observed when Rapivab was administered to subjects with renal dysfunction. Therefore, the Rapivab dose should be reduced for patients with baseline creatinine clearance below 50 mL/min using recommendations given in the product's Prescribing Information leaflet.

Rapivab is available in single-use vials containing 200 mg peramivir per 20 mL. The product should not be used if the seal over the bottle opening is broken or missing.

Patient Counseling. Specific points for patient counseling are summarized in Table 5.

Table 5
Patient counseling information for Rapivab*

Inform patients:
• that there is a risk of serious skin reactions with Rapivab use. Patients should seek immediate medical attention if a skin reaction occurs;
• that there is a risk of neuropsychiatric events in patients with influenza. Patients should contact their physician if they experience signs of abnormal behavior after receiving Rapivab.

*A complete list of information is available in the product's Prescribing Information leaflet.

Overview and Summary

These new drugs are all approved to treat potentially lethal pathologies. Continued advancement of therapies in these areas expand treatment options for patients.

• • • • • • • • • • • • • • • • •

The author, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.

This lesson is a knowledge-based CPE activity and is targeted to pharmacists in all practice settings.

Program 0129-0000-15-010-H01-P
Release date: 10-15-15
Expiration date: 10-15-18
CE Hours: 1.5 (0.15 CEU)

The Ohio Pharmacists Foundation Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

continuing education quiz

New Drugs: Lynparza, Opdivo, Rapivab and Savaysa

1. The advantages of edoxaban over warfarin include all of the following EXCEPT:
   a. more rapid onset of action.
   b. restricted dietary intake of vitamin K.
   c. fewer drug interactions.
   d. administration of fixed doses without routine coagulation monitoring.

2. The *Boxed Warning* for Savaysa warns that premature discontinuation increases the risk of:
   a. abnormal renal function. c. fetal harm.
   b. serious skin reactions. d. ischemic stroke.

3. Co-administration of edoxaban with anticogulants is never recommended.
   a. True b. False

4. All of the following are correct counseling points for Savaysa EXCEPT:
   a. to take on an empty stomach.
   b. do not double the dose when one is missed.
   c. do not discontinue without discussing with doctor.
   d. to report any unusual bleeding.

5. Nivolumab is indicated for treatment of melanoma progression following therapy with:
   a. trametinib. c. ipilimumab.
   b. dabrafenib. d. vemurafenib.

6. Melanoma is more common in:
   a. males. b. females.

7. Females receiving nivolumab should use effective contraception during therapy and following therapy for at least:
   a. one month. c. four months.
   b. two months. d. five months.

Completely fill in the lettered box corresponding to your answer.

1. [a] [b] [c] [d]	6. [a] [b]	11. [a] [b] [c] [d]
2. [a] [b] [c] [d]	7. [a] [b] [c] [d]	12. [a] [b] [c] [d]
3. [a] [b]	8. [a] [b] [c] [d]	13. [a] [b] [c] [d]
4. [a] [b] [c] [d]	9. [a] [b] [c] [d]	14. [a] [b] [c] [d]
5. [a] [b] [c] [d]	10. [a] [b] [c] [d]	15. [a] [b] [c] [d]

❑ **I am enclosing $5 for this quiz made payable to Ohio Pharmacists Association.**

1. Rate this lesson: (Excellent) 5 4 3 2 1 (Poor)
2. Did it meet each of its objectives? ❑ yes ❑ no
   If no, list any unmet_____
3. Was the content balanced and without commercial bias?
   ❑ yes ❑ no If no, why?_____
4. Did the program meet your educational/practice needs?
   ❑ yes ❑ no
5. How long did it take you to read this lesson and complete the quiz? _____
6. Comments/future topics welcome.

Please print.

Program 0129-0000-15-010-H01-P
0.15 CEU

Name_____

Address_____

City, State, Zip_____

Email_____

NABP e-Profile ID_____Birthdate_____ (MMDD)

Return quiz and payment (check or money order) to Correspondence Course, OPA, 2674 Federated Blvd, Columbus, OH 43235-4990

8. The high death rate for ovarian cancer is mostly due to:
   a. surgical complications. c. late presentation.
   b. medication side effects. d. genetic mutations.

9. Serious adverse effects of olaparib include all of the following EXCEPT:
   a. lung infection.
   b. myelodysplastic syndrome.
   c. renal dysfunction.
   d. acute myeloid leukemia.

10. The recommended dose of Lynparza is:
   a. 400 mg once daily. c. 800 mg once daily.
   b. 400 mg twice daily. d. 800 mg twice daily.

11. All of the following are true EXCEPT:
   a. influenza B can cause pandemics.
   b. influenza C is the least common.
   c. influenza viruses are single-stranded RNA viruses.
   d. the incubation period of influenza virus is 18 to 72 hours.

12. Peramivir is an inhibitor of:
   a. acetylcholinesterase. c. phosphodiesterase.
   b. tyrosine kinase. d. neuraminidase.

13. Rapivab dose should be reduced for patients with baseline creatinine clearance below:
   a. 80 mL/min. c. 60 mL/min.
   b. 70 mL/min. d. 50 mL/min.

14. Which of the following drugs carries a warning to initiate thyroid hormone replacement as needed?
   a. Lynparza c. Rapivab
   b. Opdivo d. Savaysa

15. Rash is a common side effect for all of the following EXCEPT:
   a. Lynparza. c. Rapivab.
   b. Opdivo. d. Savaysa.

To receive CE credit, your quiz must be received no later than October 15, 2018. A passing grade of 80% must be attained. CE credit for successfully completed quizzes will be uploaded to the CPE Monitor. CE statements of credit can be printed from the CPE Monitor website. Send inquiries to opa@ohiopharmacists.org.