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New Drugs: Dalvance, Entyvio, Jublia, and Zontivity

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Goal. The goal of this lesson is to provide information on dalbavancin (Dalvance™), efinaconazole (Jublia®), vedolizumab (Entyvio®) and vorapaxar (Zontivity™).

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

1. identify the new drugs by generic name, trade name and chemical name when relevant;
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 indicated to treat a wide variety of pathologies (Table 1). The lesson provides a brief introduction to the therapeutic agents, and its depth is not intended to extend beyond an overview of the topic. The reader is, therefore, urged to consult the products' full prescribing information leaflet (package insert), *Medication Guide* when available, and other reliable sources for detailed descriptions.

Dalbavancin (Dalvance)

The emergence and spread of strains of Gram-positive bacteria that are resistant to nearly all commercially available antibiotics highlight the need to develop new antibiotics to treat serious Gram-positive infections. Vancomycin (Vancocin, and others), a glycopeptide antibiotic approved for use in the U.S. to treat these infections, has been used for over three decades.

Dalbavancin is a novel semi-synthetic lipoglycopeptide antibiotic synthesized from a fermentation product of *Nonomuraea* species. Dalvance is the first drug designated as a Qualified Infectious Disease Product (QIDP) to receive FDA approval. Under the Generating Antibiotic Incentives Now (GAIN) title of the FDA Safety and Innovation Act, Dalvance was granted QIDP designation because it is an antibacterial or antifungal drug for human use intended to treat serious or life-threatening infections. As part of its designation, dalbavancin was given priority review, which provides an expedited review of the drug's application. Dalvance's (DAL-vance) QIDP designation also qualifies it for an additional five years of marketing exclusivity.

Indications and Use. Dalvance is indicated for acute bacterial skin and skin structure infections (ABSSSI) in adults caused by designated susceptible strains of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *S. agalactiae*, and *S. anginosus* group (including *S. anginosus*, *S.intermedius*, and *S. constellatus*). To reduce the development of drug-resistant bacteria and maintain the effectiveness of dalbavancin and other antibacterial drugs, Dalvance should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria.

Gram-Positive Infections. *Staphylococcus aureus* is the leading cause of bacterial infections worldwide, ranging from minor skin and soft tissue infections to more severe conditions such as pneumonia, bacteremia, complicated skin and soft-tissue infections, infective endocarditis, and diabetic foot infections. With the introduction of penicillin in the 1940s, *S. aureus* infections were routinely and successfully treated. However, within two years, penicillin-resistant strains were reported. Similarly, within two years of the introduction of methicillin, strains of methicillin-resistant *S. aureus* (MRSA) were observed.

The SENTRY Antimicrobial Surveillance Program has monitored bloodstream infections from patients in medical centers around the world since 1997. Data from 82,200 isolates compiled between 1997 to 2002 from North America, Latin America, and Europe revealed a high prevalence of multidrug-resistant Gram-positive infec-

Table 1
Selected new drugs

Generic (Trade Name)	Distributor	Indication	Dose*	Dosage Form	Most Common Side Effects	Medication Guide±
Dalbavancin (Dalvance)	Durata Therapeutics	acute bacterial skin and skin structure infections caused by certain Gram-positive organisms	1000 mg initially, then 500 mg one week later	single-use vials of 500 mg lyophilized powder for IV infusion	nausea (5.5%) headache (4.7%) diarrhea (4.4%)	No
Efinaconazole (Jublia)	Valeant Pharmaceuticals	onychomycosis of the toenails	once daily for 48 weeks	10% topical solution	(incidence >1%): ingrown toenails, dermatitis at application site, vesicles, pain	No
Vedolizumab (Entyvio)	Takeda Pharmaceuticals	moderately to severely active ulcerative colitis and Crohn's disease	300 mg at zero, 2, and 6 weeks, and then every 8 weeks	single-use vials of 300 mg lyophilized powder for IV infusion	(incidence ≥3%): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, extremity pain	Yes
Vorapaxar (Zontivity)	Merck & Co.	thrombotic cardiovascular event reduction in patients with history of MI or peripheral arterial disease	2.08 mg daily	2.08 mg tablets	bleeding, including life-threatening and fatal bleeding	Yes

*Recommended dose for most patients
±Availability at the time of publication of this lesson

tions. The resistance rate among *S. aureus* pathogens is estimated at approximately 63 percent in critically ill patients. Nearly 19,000 people in the United States died in 2005 after being infected by MRSA. Geographically, MRSA infections are most prevalent in North America, but they are also a global problem. Moreover, emergence of community-acquired MRSA (CA-MRSA) in the United States and globally has substantially altered the landscape and challenges related to these pathogens. Similarly, increases in vancomycin-resistant enterococci have been most dramatic in North America and Latin America during the past 30 years. There has also been a significant increase in these infections in Europe and parts of the developing world.

Mechanism of Action. Dalbavancin interferes with bacterial cell wall synthesis. This is accomplished by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide in nascent cell wall peptidoglycan, thus preventing cross-linking.

Efficacy and Safety. Safety and efficacy were evaluated in two clinical trials with a total of 1,269 adults with ABSSSI. Participants were randomly assigned to receive dalbavancin or vancomycin. Results showed dalbavancin was as effective as vancomycin for the treatment of ABSSSI.

The most common adverse effects identified in the clinical trials were nausea, headache, and diarrhea. The median duration of adverse reactions was four days. In the trials, more participants in the dalbavancin group had elevations in their ALT liver enzyme tests than comparator-treated patients.

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

• *Serious hypersensitivity (anaphylactic) and skin reactions have been reported with glycopeptide antibacterial agents including Dalvance*: Exercise caution in patients with known hypersensitivity to glycopeptides.

Table 2
Patient counseling information for Dalvance

Advise patients:
- that allergic reactions, including serious reactions, may occur. Serious allergic reactions require immediate treatment. Inform their healthcare provider about any previous hypersensitivity reactions to Dalvance, or other antibiotics;
- that antibacterial drugs, including Dalvance, should only be used to treat bacterial infections. They are not effective against viral infections such as the common cold;
- that diarrhea is a common adverse effect caused by antibacterial drugs. Sometimes, frequent watery or bloody diarrhea may occur. If severe watery or bloody diarrhea develops, notify their healthcare provider at once.

- *Rapid intravenous infusion of glycopeptide antibacterial agents can cause reactions.* These reactions resemble the "Red-Man Syndrome," including flushing of the upper body, urticaria, pruritus, and/or rash.
- *ALT elevations greater than three times the upper limit of normal were reported in clinical trials.*
- *Clostridium difficile-associated diarrhea has been reported with nearly all systemic antibacterial agents, including Dalvance, with severity ranging from mild diarrhea to fatal colitis*: Evaluate if diarrhea occurs.

Dalvance is **contraindicated** in patients with known hypersensitivity to dalbavancin. No data are available on cross-reactivity between dalbavancin and other glycopeptides, including vancomycin.

Drug Interactions. No clinical drug-drug interaction studies have been conducted with dalbavancin. There is minimal potential for drug-drug interactions between dalbavancin and cytochrome P450 substrates, inhibitors or inducers.

Administration, Dosing, and Availability. Dalbavancin has a half-life of 8.5 days, which makes once-weekly dosing feasible. It is a two-dose regimen administered by intravenous infusion over 30 minutes at an initial dose of 1,000 mg, followed one week later by a dose of 500 mg. Patients with creatinine clearance less than 30 mL/min should receive a reduced dosage. Dalvance is supplied in single-use vials containing 500 mg dalbavancin for reconstitution.

Patient Counseling Information. Specific points for patient counseling are summarized in Table 2.

Efinaconazole (Jublia)

Onychomycosis is a common and destructive nail infection that is currently undertreated largely because of the limitations of available treatments. It is notoriously difficult to treat and requires a long-term management program. Over-the-counter or prescription topical treatments provide limited efficacy and are often administered in conjunction with frequent debridement, or scraping, cutting or removal of the nail. Prescription oral treatments are limited by drug interactions and serious safety concerns. Existing topical antifungals are not associated with dangerous adverse events, as they rarely enter the systemic circulation and gain a significant concentration in the body. Topicals are less widely used for onychomycosis because poor penetrance into the nail plate results in correspondingly poor response. The ideal scenario would, therefore, be to develop topicals that have a higher nail plate penetrance compared with existing drugs, but maintain the advantage of minimal systemic uptake.

Indications and Use. Jublia (Joob-LEE-ah) is indicated for the topical treatment of onychomycosis of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*. These two dermatophytes are the predominant causative agents of fingernail and toenail onychomycosis, accounting for approximately 50 to 95 percent of cases, with much higher infection prevalence in toenails than in fingernails.

Onychomycosis. In early medical literature, the term *onychomycosis* traditionally referred to a nondermatophytic infection of the nail, but is now used as a general term to denote any fungal nail infection. *Tinea unguium* specifically describes a dermatophytic infection of the nail plate. In spite of the clearly diseased appearance associated with this condition, onychomycosis is all too often regarded as merely a cosmetic problem of relatively minor importance that is hardly worth the effort to resolve.

In reality, onychomycosis can have significant negative effects on the patient's emotional, social, and occupational functioning. Affected patients may experience embarrassment in social and work situations, and fear that they will transmit their infection to others. Employment can suffer if employers are reluctant to hire individuals with abnormal nails, particularly for jobs such as food handling or where interaction with the public is required. Onychomycosis can cause patients to take additional sick leave. All of the above can cause patients to stop treatment, resigning themselves to permanent disfigurement and discomfort.

In immunocompromised patients, such as those infected with HIV, onychomycosis can pose a more serious health problem. Not only does the difficult-to-treat infection serve as a constant reminder to the patient of his or her own deteriorated condition, but the possibility exists for transfer of a very high titre of fungal pathogens to others.

Mechanism of Action. Efinaconazole is an azole antifungal that inhibits fungal lanosterol 14α-demethylase involved in the biosynthesis of ergosterol, a constituent of fungal cell membranes. Ergosterol is an important structural component of fungal cell membranes, maintaining membrane fluidity and a permeability barrier, and is essential for fungal cell viability.

Efficacy and Safety. Efinaconazole was studied in two identical randomized, double-blind phase three clinical trials involving 1,655

Table 3
Patient counseling information for Julia

Advise patients:
- that Julia is for external use only, on toenails and immediately adjacent skin;
- to apply Julia once daily to clean dry toenails; wait at least 10 minutes after showering, bathing, or washing before applying;
- to inform a healthcare professional if the area of application shows signs of persistent irritation (for example, redness, itching, swelling);
- to avoid pedicures, the use of nail polish and other cosmetic nail products while using Julia;
- that the product is flammable so avoid use near heat or open flame.

patients with onychomycosis. Complete cure rates with efinaconazole were 17.8 percent in study-1 and 15.2 percent in study-2 compared with 3.3 percent and 5.5 percent, respectively, for vehicle controls. Complete cure was defined as zero percent clinical involvement of the target toenail, as well as negative potassium hydroxide examination and fungal culture at week 52. Mycologic cure rates (negative nail culture and microscopy results) were also significantly better with efinaconazole, at 55.2 percent and 53.4 percent, compared to controls.

Adverse events that were reported were generally mild and transient and were similar between patients treated with efinaconazole and those treated with vehicle controls. The most commonly reported adverse events (>1 percent) in patients treated with efinaconazole were application site dermatitis, vesicles, and pain.

Warnings, Precautions, and Contraindications. There are none listed for efinaconazole.

Drug Interactions. Efinaconazole is a non-inhibitor of the CYP450 enzyme family. In *in vitro* studies using human liver microsomes, efinaconazole did not inhibit CYP1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2PE1 and 3A4 activities. *In vitro* studies in human primary hepatocytes showed that efinaconazole did not induce CYP1A2 or 3A4 activities.

Administration, Dosing, and Availability. Julia is applied to affected toenails once daily for 48 weeks, using the integrated flow-through brush applicator. When applying it, ensure the toenail, toenail folds, toenail bed, hyponychium (commonly called the "quick," this is a bed of soft tissue that lies under the free portion of the nail at the end of the digit), and the undersurface of the toenail plate are completely covered. The solution dries quickly, and there is no need to remove excess product. Julia is for topical use only and not for oral, ophthalmic, or intravaginal use. Julia is available as a topical solution containing 10 percent efinaconazole.

Patient Counseling Information. Specific points for patient counseling are summarized in Table 3.

Vedolizumab (Entyvio)

Crohn's disease (CD) and ulcerative colitis (UC), collectively known as inflammatory bowel disease (IBD), affect more than one million persons in the United States and several additional million worldwide. The precise cause of these inflammatory disorders remains unknown, but major advances in understanding the mechanisms of chronic intestinal inflammation have produced a number of new biologic therapies. The prototypic biologic approach in patients with IBD is the use of monoclonal antibodies that target the proinflammatory cytokine tumor necrosis factor (TNF) with anti-TNF drugs that include infliximab (Remicade), adalimumab (Humira), and certolizumab pegol (Cimzia). Approval of Entyvio (en-TI-vee-oh), which is not a TNF antagonist, provides an important new treatment option for patients with IBD.

Indications and Use. Entyvio is indicated for treatment of adult patients with moderately to severely active UC or CD, who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. Goals of therapy for UC with vedolizumab include inducing and maintaining clinical response and remission, improving endoscopic appearance of the mucosa, and achieving corticosteroid-free remission. Goals for CD are achieving clinical responses and remission, and achieving corticosteroid-free remission.

Inflammatory Bowel Disease. Circulating leukocytes are crucial in the pathogenesis of IBD and are important targets for drug development. T-lymphocyte cells travel from the blood, to the gut mucosa, and back into the blood and primary lymphoid organs. Adhesion molecules regulate this cornerstone phenomenon known as T-cell trafficking. Inhibition of leukocyte trafficking to the intestinal mucosa is an alternate target to antagonizing TNF for development of drugs to treat IBD. Blocking antibodies inhibit the interaction between leukocytes and the intestinal vasculature, thereby decreasing influx of inflammatory cells into affected gastrointestinal tissues. One such antibody, natalizumab (Tysabri), targets both the $\alpha_4\beta_7$ and $\alpha_4\beta_1$ integrins that control leukocyte adhesion to the vascular endothelium. Natalizumab received approval in 2008 for treatment of CD and multiple sclerosis; however, its use was subsequently limited by its potential to lead to progressive multifocal leukoencephalopathy (PML), an opportunistic viral infection of the brain.

Mechanism of Action. Vedolizumab, a humanized immunoglobulin monoclonal antibody, is an integrin receptor antagonist that blocks the entire $\alpha_4\beta_7$ integrin and does not affect $\alpha_4\beta_1$-mediated leukocyte trafficking to the nervous system, thus potentially reducing the risk of PML. No cases of PML were observed throughout the clinical trials that examined vedolizumab for efficacy. Integrin receptors are proteins expressed

on the surface of certain cells and function as bridges for cell-cell interactions. Vedolizumab blocks the interaction of a specific integrin receptor (expressed on circulating inflammatory cells) with a specific protein (expressed on cells in the interior wall of blood vessels), and thereby blocks the migration of those circulating inflammatory cells across those blood vessels and into areas of inflammation in the gastrointestinal tract.

Efficacy and Safety. Two separate phase 3, placebo-controlled studies investigated efficacy and safety issues of vedolizumab. The trials, together, involved 2,010 patients. Primary and secondary efficacy end points were met in the UC study, with a 47 percent clinical response rate at week 6 among subjects receiving vedolizumab, compared with 26 percent among those who received placebo. Among patients who responded to vedolizumab, 42 to 45 percent of those who continued to receive the medication were in remission at week 52, compared with 16 percent of those who received the placebo.

Vedolizumab was less efficacious at inducing a clinical response in patients with CD, with a 31 percent response rate at week 6 vs. 26 percent with placebo. The vedolizumab-treated group showed benefit in maintaining remission (36 to 39 percent at week 52 vs. 22 percent with placebo).

The most common adverse effects in patients treated with vedolizumab included headache, joint pain, nausea, and fever. The most serious risks included serious infections, hypersensitivity and infusion-related reactions, and hepatotoxicity.

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

• *Hypersensitivity reactions, including anaphylaxis*: Discontinue the drug if anaphylaxis or other serious allergic reactions occur.

• *Infections*: Treatment with Entyvio is not recommended in patients with active, severe infections until the infections are controlled. The most common infections in clinical trials, occurring at a greater rate with Entyvio than placebo, involved the upper respiratory and nasal mucosa. Serious infections have also been reported, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, *Listeria meningitis*, giardiasis and cytomegaloviral colitis. Consider withholding the drug in patients who develop a severe infection while treated with Entyvio.

• *Progressive Multifocal Leukoencephalopathy (PML)*: Although no cases have been observed in clinical trials with Entyvio, PML has occurred in patients treated with another integrin receptor antagonist. Monitor patients for any new or worsening neurological signs or symptoms.

Entyvio is **contraindicated** in patients who have had a known serious or severe hypersensitivity reaction (such as dyspnea, bronchospasm, urticaria, flushing, rash, and increased heart rate) to Entyvio or any of its excipients.

Drug Interactions. Because of the potential for increased risk of PML and other infections, avoid the concomitant use of Entyvio with natalizumab. Because of the potential for increased risk of infections, avoid concomitant use with TNF blockers. Live vaccines may be administered concurrently with Entyvio only if the benefits outweigh the risks.

Administration, Dosing, and Availability. Entyvio is available as single-use 20 mL vials containing 300 mg of lyophilized vedolizumab. The recommended dosage in UC and CD is 300 mg infused intravenously over approximately 30 minutes at zero, two and six weeks, then every eight weeks thereafter. Dosage should be discontinued in patients who do not show evidence of therapeutic benefit by week 14. Patients should be brought up to date with all immunizations (according to current immunization guidelines) before initiating treatment with vedolizumab.

Table 4
Patient counseling information for Entyvio

Advise patients:
• to read the FDA-approved *Medication Guide* each time they are scheduled to receive a dose;
• to tell their healthcare provider right away if they experience symptoms of hypersensitivity reaction during or following infusion;
• that they may be more likely to develop infections when taking Entyvio, and to report any signs or symptoms of infection to their healthcare provider;
• that PML has occurred in patients who received a different integrin receptor antagonist product, and to report any new onset or worsening of neurological signs and symptoms immediately;
• that elevated transaminase levels, with or without elevated bilirubin, have occurred with this drug, and to report fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice immediately to their healthcare provider.

Patient Counseling Information. Due to the PML warning associated with natalizumab for CD, many patients are concerned about potential adverse events. Now that a new anti-adhesion drug, vedolizumab, has been proven effective in IBD, patients' questions about its safety will likely continue. Vedolizumab, unlike natalizumab, is designed to be specific to the gut integrin complex, $\alpha_4\beta_7$. Although clinical trials suggest that vedolizumab does not affect the CNS, questions persist about whether the risk of PML with this new molecule will be completely avoided.

An FDA-approved *Medication Guide* must be dispensed with each prescription and refill for Entyvio. Specific points for counseling are summarized in Table 4.

Vorapaxar (Zontivity)

Vorapaxar is the first in a new drug class called protease-activated receptor-1 (PAR-1) antagonists. It is an antiplatelet agent, designed to decrease the tendency of plate-

lets to clump together to form a thrombus. By antagonizing the formation of thrombi, vorapaxar helps decrease the risk of myocardial infarction (MI) and stroke.

Indications and Use. Zontivity (zon-TIV-iti) is indicated for the reduction of thrombotic cardiovascular events in patients with a history of MI or peripheral arterial disease. The drug has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and need for urgent coronary revascularization.

Blood Platelets in Atherothrombotic Disease. Platelets play a crucial role in primary hemostasis and vascular repair. They are also vital to the pathogenic formation of thrombi that are responsible for clinical manifestations of atherothrombotic disease. Numerous pathways stimulated by specific agonists, such as adenosine diphosphate (ADP), thromboxane A_2, and thrombin (the most potent platelet activity), contribute to platelet activation, which is important in pathologic thrombosis, as well as hemostasis. The key role of platelet activation in the pathophysiology of atherothrombotic disease is supported by the well-established clinical benefit of antiplatelet therapy. Currently employed antiplatelet agents, such as aspirin and $P2Y_{12}$ receptor antagonists (i.e., clopidogrel [Plavix], ticlopidine [Ticlid], and prasugrel [Effient]), inhibit the thromboxane A_2 and ADP platelet activation pathways. Although dual antiplatelet therapy can result in a greater clinical benefit than either drug alone, and despite improvement in morbidity and mortality with the use of current antiplatelet agents, many patients remain at significant risk for recurrent ischemic complications. This high number can be attributed to the drugs' lack of inhibitory activity on other platelet activation pathways. Moreover, the use of aspirin and $P2Y_{12}$ receptor antagonists is associated with significantly increased risk of hemorrhage, which may contribute to both short-term and long-term morbidity and mortality.

This bleeding risk with aspirin and $P2Y_{12}$ receptor antagonists may result from the drugs targeting pathways that are involved in both pathologic thrombosis as well as protective hemostasis. Therefore, a critical need exists for new drugs with alternate mechanisms of action that reduce thrombosis without interfering with hemostasis. Inhibition of PAR-1, the primary receptor site for thrombin on platelets, represents one such strategy for prevention of platelet activation with thrombosis. The binding of thrombin to PAR-1 is a potent platelet activation pathway that is necessary for thrombus formation, but has also been shown to not be required for hemostasis.

Inhibition of PAR-1 may prevent pathologic thrombosis with the added advantage of not causing a significant inhibitory effect on beneficial hemostasis, thereby potentially reducing the risk of ischemic cardiovascular events without increasing the risk of hemorrhage. Given the favorable profile of noninterference with hemostasis, the drug can be used in combination with thromboxane A_2 and ADP inhibitors, thereby further reducing the incidence of thrombosis.

Mechanism of Action. Vorapaxar is a novel antiplatelet agent that selectively antagonizes PAR-1 expressed on platelets, but its long half-life makes it effectively irreversible. Vorapaxar inhibited thrombin-induced and thrombin receptor agonist peptide (TRAP)-induced platelet aggregation in *in vitro* studies. The drug does not inhibit platelet aggregation induced by ADP, collagen, or a thromboxane mimetic. PAR-1 receptors are also expressed in a wide variety of cell types, including endothelial cells, neurons, and smooth muscle cells, but its pharmacodynamic activities in these cell types have not been assessed.

Efficacy and Safety. In the study that supported the drug's approval, Zontivity lowered the risk of thrombosis from 9.5 percent to 7.9 percent over a three-year period – about 0.5 percent per year. When added to other anti-platelet agents (generally aspirin and clopidogrel) in a trial involving more than 25,000 subjects, Zontivity reduced the rate of a combined endpoint of heart attack, stroke, cardiovascular death, and need for coronary revascularization when compared to a placebo.

Bleeding is the most commonly reported adverse reaction in patients taking Zontivity, even though bleeding is less common than with some other antiplatelet drugs. The drug's prescribing information includes a *Boxed Warning* to alert healthcare professionals about this risk. General risk factors for bleeding include older age, low body weight, reduced renal or hepatic function, history of bleeding disorders, and use of certain concomitant medications (e.g., anticoagulants, fibrinolytic therapy, chronic NSAIDs, and selective serotonin reuptake inhibitors).

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

• *Increased risk of bleeding*: Bleeding may be life-threatening and fatal. The drug must be discontinued in patients who experience a stroke, TIA or intracranial hemorrhage (ICH). Withholding the drug for a brief period will not be useful in managing an acute bleeding event because of its long half-life (three to four days, with an apparent terminal elimination half-life of eight days). There is no known treatment to reverse the antiplatelet effect of Zontivity. Significant inhibition of platelet aggregation remains four weeks after discontinuation.

• *Strong CYP3A inhibitors or inducers:* Strong CYP3A inhibitors increase and inducers decrease Zontivity exposure. Avoid concomitant use.

Contraindications include a history of stroke, TIA, or ICH, because of an increased risk of ICH in this population, and active pathologic bleeding such as peptic ulcer disease.

Table 5
Patient counseling information for Zontivity

Advise patients:
- to read the FDA-approved *Medication Guide* with each new or refilled prescription;
- to take the medicine exactly as prescribed and not to discontinue it without talking with their physician;
- about the benefits and potential adverse effects of Zontivity;
- that they may bleed and bruise more easily when taking Zontivity, and to report any unanticipated, prolonged, or excessive bleeding or blood in their stool or urine;
- that they should inform physicians and dentists that they are taking Zontivity before any surgery or dental procedure, and the prescriber should be informed before stopping Zontivity;
- to list all prescription medications, over-the-counter medications, or dietary supplements they are taking, or plan to take, in order to avoid drugs that may affect bleeding risk.

Drug Interactions. Vorapaxar is eliminated primarily by metabolism, with contributions from CYP3A and CYP2J2. Avoid concomitant use of vorapaxar with strong inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, telaprevir, telithromycin, and conivaptan) and strong inducers of CYP3A (e.g., rifampin, carbamazepine, St. John's Wort, and phenytoin).

Administration, Dosing, and Availability. The dose of vorapaxar is one tablet orally once daily, with or without food. There is limited clinical experience with other antiplatelet drugs or with vorapaxar as the only antiplatelet agent. Use with aspirin and/or clopidogrel according to their indications or standard of care. Zontivity tablets contain 2.08 mg vorapaxar, which is equivalent to 2.5 mg of vorapaxar sulfate.

Patient Counseling Information. An FDA-approved *Medication Guide* must be dispensed with each prescription and refill for Zontivity. Specific points for counseling are summarized in Table 5.

Overview and Summary

These four new-molecular entity drugs have been approved to treat a wide variety of indications. Each has been demonstrated to be effective and safe when used as directed. Both efficacy and safety can be maximized when healthcare providers counsel patients well.

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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.

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continuing education quiz

New Drugs: Dalvance, Entyvio, Jublia, and Zontivity

1. Aside from dalbavancin, which of the following drugs is a glycopeptide approved in the U.S. to treat Gram-positive infections?
   a. Ciprofloxacin c. Vancomycin
   b. Clarithromycin d. Mupirocin

2. The first drug designated as a Qualified Infectious Disease Product to receive FDA approval is:
   a. dalbavancin. c. ciprofloxacin.
   b. efinaconazole. d. daptomycin.

3. The leading cause of bacterial infections worldwide is:
   a. *S. pyogenes*. c. *S. agalactiae*.
   b. *S. anginosus*. d. *S. aureus*.

4. Dalbavancin acts by:
   a. inhibiting protein synthesis.
   b. interfering with bacterial cell wall synthesis.
   c. inhibiting lanosterol 14α-demethylase.
   d. inactivating ß-lactamase enyzmes.

5. The reported half-life of dalbavancin is:
   a. 2.5 days. c. 8.5 days.
   b. 4.5 days. d. 12.5 days.

6. Jublia is applied to affected toenails once daily for:
   a. 4 weeks. c. 36 weeks.
   b. 24 weeks. d. 48 weeks.

7. All of the following are true about onychomycosis EXCEPT:
   a. it is a common and destructive affliction of the nails.
   b. treatment requires a long-term management program.
   c. infection prevalence is higher in fingernails than in toenails.
   d. it is a general term denoting any fungal nail infection.

Completely fill in the lettered box corresponding to your answer.

1.	[a]	[b]	[c]	[d]	6.	[a]	[b]	[c]	[d]	11.	[a]	[b]	[c]	[d]
2.	[a]	[b]	[c]	[d]	7.	[a]	[b]	[c]	[d]	12.	[a]	[b]	[c]	[d]
3.	[a]	[b]	[c]	[d]	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_____
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   ❑ yes ❑ no
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8. Vedolizumab is classified as a/an:
   a. tumor necrosis factor antagonist.
   b. integrin receptor antagonist.
   c. protease-activated receptor-1 antagonist.
   d. janus kinase receptor agonist.

9. The following drug should not be used concomitantly with Entyvio.
   a. Natalizumab c. Methotrexate
   b. Droxidopa d. Vorapaxar

10. A *Boxed Warning* is included in Zontivity 's prescribing information for:
   a. headache. c. diarrhea.
   b. bleeding. d. constipation.

11. All of the following are true for vorapaxar EXCEPT:
   a. it selectively antagonizes PAR-1.
   b. its long half-life makes it effectively irreversible.
   c. it inhibits platelet aggregation induced by collagen.
   d. it does not inhibit platelet aggregation induced by ADP.

12. Which of the following medications is infused intravenously at zero, two and six weeks, and then every eight weeks?
   a. Dalvance c. Jublia
   b. Entyvio d. Zontivity

13. Progressive multifocal leukoencephalopathy is a warning/precaution for:
   a. Dalvance. c. Jublia.
   b. Entyvio. d. Zontivity.

14. Before surgery or dental procedures, patients should be counseled to inform their physicians and dentists that they are taking:
   a. Dalvance. c. Jublia.
   b. Entyvio. d. Zontivity.

15. Patients should be advised to keep the following product away from heat or open flame.
   a. Dalvance c. Jublia
   b. Entyvio d. Zontivity

To receive CE credit, your quiz must be received no later than March15, 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.