Objective: To provide information regarding the most important properties of new therapeutic agents that have been marketed in 2014.

Data sources: Product labeling supplemented selectively with published studies and drug information reference sources.

Data synthesis: Seven new therapeutic agents that were marketed in the United States in early 2014 are considered in this first of a four-part series: umeclidinium bromide/vilanterol, perampanel, eslicarbazepine acetate, apremilast, dapagliflozin propanediol, avanafil, and bazedoxifene/conjugated estrogens. Indications and information on dosage and administration for these agents are reviewed, as are the most important pharmacokinetic properties, drug interactions, and other precautions. Practical considerations for use of these new agents are also discussed. When possible, properties of the new drugs are compared with those of older agents marketed for the same indications.

Conclusion: Umeclidinium/vilanterol is the first combination formulation for oral inhalation to include both a long-acting muscarinic antagonist and a long-acting beta-2-adrenergic agonist for the maintenance treatment of patients with chronic obstructive pulmonary disease. Both perampanel and eslicarbazepine have been approved as adjunctive treatment for patients with partial-onset seizures. Perampanel has a unique mechanism of action whereas eslicarbazepine has properties that are most similar to those of oxcarbazepine. Apremilast is indicated for the treatment of patients with active psoriatic arthritis and is effective following oral administration. Dapagliflozin is the second sodium-glucose cotransporter 2 inhibitor to be approved for the treatment of patients with type 2 diabetes, and has properties that are most similar to those of canagliflozin. Avanafil is the fourth phosphodiesterase type 5 inhibitor to be approved for the treatment of men with erectile dysfunction and may have a faster onset of action than the other agents. Bazedoxifene is an estrogen agonist/antagonist that is used in combination with conjugated estrogens for the treatment of women with moderate-to-severe vasomotor symptoms associated with menopause and for the prevention of postmenopausal osteoporosis.

Keywords: New drugs, Food and Drug Administration, drug development, pharmaceutical marketing, risk assessment.

New therapeutic agents marketed in 2014: Part 1
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Learning objectives:
At the conclusion of this knowledge-based activity, the pharmacist will be able to:
- Identify new therapeutic agents that are considered and explain their appropriate use.
- Identify indications, most important adverse events, and other risks of each new therapeutic agent.
- State route of administration for each new drug and important considerations regarding dosage and administration.
- Demonstrate appropriate patient counseling regarding use of the new medications and precautions to be observed.
Bronchodilator

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States. Cigarette smoking is the most common cause. The maintenance treatment of COPD often involves the use of a long-acting beta-2-adrenergic agonist (LABA; i.e., salmeterol [Serevent], formoterol [Foradil], indacaterol [Arcapta], vilanterol [in combination with fluticasone—Breo Ellipta]) and/or a long-acting muscarinic antagonist (LAMA; i.e., tiotropium [Spiriva HandiHaler], aclidinium [Tudorza Pressair]) via oral inhalation. Both the LABAs and LAMAs provide a bronchodilating action and an inhaled corticosteroid may also be added to the regimen.

Umeclidinium bromide joins tiotropium and aclidinium in the group of LAMAs, also designated as long-acting anticholinergic or antimuscarinic agents. It was initially approved in a formulation with the LABA vilanterol trifenate (Anoon Ellipta—GlaxoSmithKline), and is the first combination formulation to include both a LAMA and LABA. Therefore, patients who do not experience adequate benefit with the use of one inhaled bronchodilator can be treated with two bronchodilators with different mechanisms of action with one dose from the same delivery device. Although a combination formulation (Combivent Respimat) of ipratropium and albuterol is also available, these agents have a shorter duration of action and must be administered more frequently.

The umeclidinium/vilanterol combination is administered by oral inhalation and its specific indication is for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The effectiveness of the combination was demonstrated in studies in which the new formulation provided a larger increase in forced expiratory volume in the first second of expiration (FEV1) at 24 weeks than either of the individual components or placebo.

The indication for tiotropium also includes use for reducing COPD exacerbations. However, this is not a labeled indication for umeclidinium/vilanterol or for aclidinium. The new combination formulation is not indicated for the relief of acute bronchospasm or in patients with acutely deteriorating COPD, or for the treatment of asthma.

The risks and precautions with the use of umeclidinium/vilanterol are very similar to those of the other LAMAs and LABAs that are administered by oral inhalation. The product is contraindicated in patients with severe hypersensitivity to milk proteins or any other ingredients of the formulation. Paradoxical bronchospasm has been experienced infrequently and treatment should be discontinued if this response occurs. Because of its anticholinergic action, umeclidinium may cause worsening of urinary retention or narrow-angle glaucoma, and patients should be advised to immediately consult their physician if signs or symptoms of these complications occur. The activity of umeclidinium may be increased by the use of other medications with anticholinergic activity (e.g., tolterodine [e.g., Detrol], diphenhydramine [e.g., Benadryl]), and the concurrent use of these agents should be avoided.

Other precautions must also be observed because of the inclusion of vilanterol in the formulation. Like the other LABAs, its use is associated with an increased risk of asthma-related death, and this is the subject of a boxed warning in its labeling, as well as multiple observations that the new product is not indicated for the treatment of asthma. The beta-2 agonists must also be used with caution in patients with cardiovascular disorders, convulsive disorders, thyrotoxicosis, and diabetes. The new product should not be used concurrently with another LABA because of the risk of an excessive response. A beta-adrenergic blocking agent can inhibit the bronchodilating action of vilanterol and may produce severe bronchospasm. Accordingly, concurrent use is best avoided. Vilanterol is a substrate for the CYP3A4 pathway and its exposure and activity may be increased by the concurrent use of ketoconazole or another strong CYP3A4 inhibitor (e.g., clarithromycin). Caution must be exercised if a CYP3A4 inhibitor is used concomitantly with umeclidinium/vilanterol. The risk of cardiovascular adverse events may be increased by a monoamine oxidase inhibitor or tricyclic antidepressant. Their concurrent use with vilanterol or another beta-agonist is best avoided but, if treatment with the potentially interacting drugs is considered necessary, extreme caution must be exercised.

The most commonly experienced adverse events in the clinical studies of umeclidinium/vilanterol include pharyngitis (2%), diarrhea (2%), and pain in extremity (2%). The product is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the
risk to the fetus. COPD does not usually occur in children and the effectiveness and safety of the new product in pediatric patients have not been established.

Following oral inhalation, both umeclidinium and vilanterol are mostly absorbed from the lung with minimum contribution from oral absorption. Umeclidinium is a substrate for the CYP2D6 metabolic pathway and the P-glycoprotein transporter. However, clinically important pharmacokinetic interactions involving umeclidinium are unlikely. Patients with impaired hepatic or renal function experience little change in exposure of umeclidinium.

Umeclidinium bromide and vilanterol trifenate are supplied in a plastic inhaler containing two double-foil blister strips, each with 30 blisters. An institutional pack containing seven blisters per strip is also available. Each blister on one strip contains a powder mix that includes micronized umeclidinium bromide in an amount equivalent to 62.5 mcg of umeclidinium. Each blister on the other strip contains a powder mix that includes micronized vilanterol trifenate in an amount equivalent to 25 mcg of vilanterol. When the inhaler is activated, the powder within both blisters is exposed and available for dispersion into the airstream created by the patient inhaling through the mouthpiece. The powder mixes of the two drugs also include lactose monohydrate, which contains milk proteins.

The recommended dosage of umeclidinium/vilanterol is one oral inhalation containing 62.5 mcg of umeclidinium and 25 mcg of vilanterol once a day. The product should be administered at the same time every day, and should not be used more than once every 24 hours.

The umeclidinium/vilanterol inhalation system is supplied in a moisture-protective foil tray and should be removed from the tray only immediately before initial use. The inhaler should be discarded when the dose counter reads “0” after all blisters have been used (presumably after 30 days when used once daily, as recommended) or six weeks after opening the foil tray, whichever comes first.

Subsequent to the approval of the combination of umeclidinium and vilanterol, FDA approved a formulation of umeclidinium as a single agent (Incruse Ellipta) for oral administration. Vilanterol continues to be available only in combination formulations (Anoro Ellipta and Breo Ellipta).

**Antiepileptic drugs**

Two new drugs have been marketed for the treatment of partial-onset seizures, the most common type of seizure experienced by people with epilepsy. Partial seizures affect only a limited or localized area of the brain, but can spread to other parts of the brain. The two new antiepileptic drugs (AEDs) are considered individually in the following discussions.

**Perampanel** (Fycompa—Eisai) is a noncompetitive antagonist of the ionotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on postsynaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS) and is implicated in a number of neurological disorders caused by neuronal overexcitation. Perampanel is the first AED with this mechanism of action, although the precise manner in which it provides its antiepileptic action has not been determined.

Perampanel is indicated as adjunctive therapy for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy, aged 12 years and older. Its effectiveness was demonstrated in three placebo-controlled studies in patients who had a mean duration of epilepsy of approximately 21 years, a median baseline seizure frequency ranging from 9.3 to 14.3 seizures per 28 days, and who typically were also taking two to three concomitant AEDs. The primary endpoint in the three studies was the percent change in seizure frequency per 28 days during the treatment period as compared with the baseline period. The results from the studies showed improvement in seizure control in patients treated with perampanel compared with those receiving placebo. Approximately 50% of the patients in the studies were also taking at least one AED that is known to induce the CYP3A metabolic pathway (carbamazepine, oxcarbazepine, or phenytoin) and cause a significant reduction in the serum concentration of perampanel.

The most important concern with the use of perampanel is the risk of serious psychiatric and behavioral reactions.

### Table 1. New therapeutic agents marketed in the United States in 2014: Part 1

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Therapeutic classification</th>
<th>Route of administration</th>
<th>FDA classification*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apremilast</td>
<td>Oleza</td>
<td>Celgene</td>
<td>Anti-inflammatory agent</td>
<td>Oral</td>
<td>1-S</td>
</tr>
<tr>
<td>Avanafil</td>
<td>Stendra</td>
<td>Auxilium; Vivus</td>
<td>Agent for erectile dysfunction</td>
<td>Oral</td>
<td>1-S</td>
</tr>
<tr>
<td>Bazedoxifene/ conjugated estrogens</td>
<td>Duavee</td>
<td>Pfizer</td>
<td>Agent for menopause-associated conditions</td>
<td>Oral</td>
<td>1, 4-S</td>
</tr>
<tr>
<td>Dapagliflozin propanediol</td>
<td>Farxiga</td>
<td>Bristol-Myers Squibb; AstraZeneca</td>
<td>Antidiabetic agent</td>
<td>Oral</td>
<td>1-S</td>
</tr>
<tr>
<td>Esllicarbazepine acetate</td>
<td>Aptorn</td>
<td>Sunovion</td>
<td>Antiepileptic drug</td>
<td>Oral</td>
<td>1-S</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Fycompa</td>
<td>Eisai</td>
<td>Antiepileptic drug</td>
<td>Oral</td>
<td>1-S</td>
</tr>
<tr>
<td>Umeclidinium bromide/vilanterol trifenate</td>
<td>Anoro Ellipta</td>
<td>GlaxoSmithKline</td>
<td>Bronchodilator</td>
<td>Oral inhalation</td>
<td>1, 4-S</td>
</tr>
</tbody>
</table>

*FDA classification of new drugs: 1 = new molecular entity; 4 = combination product; S = standard review
and these are the subject of a boxed warning in its labeling. Reactions may include aggression, hostility, irritability, anger, and homicidal ideation and threats. Patients should be monitored for these reactions, as well as for changes in mood, behavior, or personality that are not typical for the patient, particularly during the titration period and at higher doses. If such symptoms occur, the dosage should be reduced, and the drug should be discontinued immediately if symptoms are severe or are worsening.

AEDs, including perampanel, have been associated with an increased risk of suicidal thoughts or behavior. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

The most frequently experienced adverse events in the clinical studies of perampanel (and their incidence with a dosage of 8 mg daily) include dizziness (32%), somnolence (16%), fatigue (8%), irritability (7%), nausea (6%), balance disorder (5%), falls (5%), gait disturbance (4%), weight gain (4%), vertigo (3%), and ataxia (3%). The frequency of neurologic effects (e.g., dizziness, somnolence, and falls) warrants particular caution in elderly patients who are at increased risk of these events. Patients should be advised against engaging in potentially hazardous activities, such as driving or operating machinery, until they have assessed how they respond to the CNS effects of the drug. Neurologic effects were most often responsible for discontinuation of treatment because of an adverse event which occurred in 8% and 19% of patients treated with 8 mg/day and 12 mg/day, respectively, compared with 5% of those receiving placebo. The concurrent use of alcoholic beverages or other CNS depressants is likely to have an additive or supra-additive CNS response.

Studies of the abuse potential of perampanel have demonstrated an incidence of euphoria that is higher than with alprazolam but lower than with ketamine. Its potential to produce withdrawal symptoms has not been adequately studied. The new drug has been classified as a Schedule III controlled substance.

Perampanel is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. If it is considered important to use perampanel during pregnancy, patients should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry (1-888-233–2334). The effectiveness and safety of perampanel in patients younger than 12 years have not been established.

Following oral administration, perampanel is rapidly and completely absorbed. Food does not affect the extent of absorption, but slows the rate of absorption. The drug is extensively metabolized via primary oxidation mediated by CYP3A4 and CYP3A5, and sequential glucuronidation. Approximately one-half of a dose is recovered in the feces and one-quarter in the urine. The dosage should be reduced in patients with mild or moderate hepatic impairment. The use of perampanel in patients with severe hepatic or renal impairment, or in patients undergoing hemodialysis, is not recommended.

The concomitant use of known CYP inducers including other AEDs such as oxcarbazepine reduces the plasma concentration of perampanel by one-half to two-thirds. A higher dosage of perampanel should be used when initiating treatment in patients already being treated with enzyme-inducing AEDs. The use of other strong CYP3A inducers such as rifampin and St. John’s wort should be avoided in patients treated with perampanel.

The use of perampanel in a dosage of 12 mg/day has been reported to reduce levonorgestrel exposure by approximately 40%. When perampanel is used in women using contraceptives containing levonorgestrel, additional nonhormonal forms of contraception should be recommended.

In patients who are not also being treated with enzyme-inducing AEDs, the recommended starting dosage of perampanel is 2 mg once a day at bedtime. The dosage may be increased by 2 mg per day increments no more frequently than every week to a dose of 4–8 mg once a day at bedtime. In elderly patients, dosage increases during titration are recommended no more frequently than every two weeks.

The recommended maintenance dosage range is 8–12 mg once a day. A dosage of 12 mg once a day resulted in somewhat greater reductions in seizure rates than the dose of 8 mg once a day, but with a substantial increase in adverse events. The dosage for individual patients should be adjusted based on clinical response and tolerability.

In patients whose AED regimen includes an enzyme-inducing drug (e.g., carbamazepine, oxcarbazepine, and phenytoin), the recommended starting dosage of perampanel is 4 mg once a day. The effect of perampanel on seizure rates was significantly reduced in these patients in the clinical studies, but the reduction in seizure frequency was somewhat greater at a dosage of 12 mg a day than at 8 mg a day. When an enzyme-inducing AED is introduced or withdrawn from a treatment regimen, patient response and tolerability should be closely monitored, and dosage adjustment may be necessary.

In patients with moderate renal impairment, a slower dosage titration should be considered. The product labeling should be consulted for the dosage recommendations for perampanel in patients with mild or moderate hepatic impairment.

Perampanel tablets are supplied in 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg potencies. Eslicarbazepine acetate (Aptiom—Sunovion) has properties that are most similar to those of oxcarbazepine (e.g., Trileptal) and carbamazepine (e.g., Tegretol, Carbatrol). Following oral administration, it is extensively converted to eslicarbazepine, which is responsible for its therapeutic effects. Eslicarbazepine is the S-isomer of the active metabolite of oxcarbazepine. The anticonvulsant activity of these agents is thought to involve inhibition of voltage-gated sodium channels.
channels, although their precise mechanism of action is not known.

Eslicarbazepine is indicated as adjunctive treatment of partial-onset seizures. Its effectiveness was demonstrated in three placebo-controlled studies in patients who had a median duration of epilepsy of 19 years, a median baseline seizure frequency of eight seizures per 28 days, and who were also taking one or two concomitant AEDs. The most commonly used AEDs were carbamazepine, lamotrigine, and valproic acid. Oxcarbazepine was not permitted as a concomitant AED. The primary efficacy endpoint in the three studies was the standardized seizure frequency over 28 days during the treatment period as compared with the baseline period. Eslicarbazepine was effective in reducing the frequency of seizures in each of the three studies. However, in the largest study (approximately 600 participants), the reduction in seizure frequency over 28 days was considered statistically significant only for the dosage of 1200 mg/day (6.0 compared to 7.9 with placebo), and not for the dosage of 800 mg/day (6.5 compared to 7.9).

Oxcarbazepine is also indicated for use as monotherapy in patients with partial-onset seizures, as well as for use in pediatric patients (2 years and older). However, these are not labeled indications for eslicarbazepine at the present time.

The use of eslicarbazepine is contraindicated in patients with a hypersensitivity to it or oxcarbazepine. There have been reports of anaphylaxis, angioedema, serious dermatologic reactions, including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity with the use of eslicarbazepine. If a patient experiences any of these reactions that is not attributable to another causative factor, eslicarbazepine should be discontinued. The new drug should not be used in patients who have experienced prior reactions of this type with either it or oxcarbazepine.

AEDs, including eslicarbazepine, increase the risk of suicidal thoughts or behavior (estimated to occur in approximately 1 in 500). Patients should be monitored for changes in mood or behavior, or other indicators that might suggest greater risk.

The most frequently experienced adverse events in the clinical studies of eslicarbazepine (and their incidence with a dosage of 800 mg daily) include dizziness (20%), headache (13%), somnolence (11%), nausea (10%), diplopia (9%), blurred vision (6%), vomiting (6%), fatigue (4%), ataxia (4%), vertigo (2%), and tremor (2%). The rate of discontinuation of treatment because of an adverse event was 14% and 25% in patients treated with dosages of 800 mg/day and 1200 mg/day, respectively, compared with 7% of those receiving placebo.

There appears to be an increased risk of neurologic adverse events such as dizziness during the dosage titration period, and an increased risk is also likely in the elderly. The incidence of dizziness was higher in patients who were also treated with carbamazepine as part of their AED regimen, and dosage modifications of both drugs should be considered. Dose-dependent increases in cognitive dysfunction-related events (e.g., memory impairment and disorientation) have also been associated with the use of eslicarbazepine. Patients should be cautioned regarding the risk of concurrent use of other agents that have CNS effects, including alcoholic beverages, and advised against engaging in activities such as driving or operating dangerous machinery until they have assessed how they respond to the CNS effects of the drug.

Some patients have experienced hyponatremia during treatment with eslicarbazepine, and the measurement of serum sodium and chloride concentrations should be considered, particularly if the patient is taking other medications known to reduce sodium concentrations. Abnormalities in liver function tests and thyroid function tests have also been reported, and baseline evaluations of liver function tests are recommended. Treatment with eslicarbazepine should be discontinued in patients with jaundice or evidence of significant liver injury.

Eslicarbazepine is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. Pregnant women who are being treated with the new drug should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry (1–888–233–2334). Eslicarbazepine is excreted in human milk, and a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of eslicarbazepine in patients younger than 18 years have not been established.

Following oral administration, eslicarbazepine acetate is highly bioavailable, and food has no effect on its pharmacokinetic characteristics. It is rapidly and extensively metabolized by hydrolytic first-pass metabolism to eslicarbazepine, and this metabolite provides more than 90% of systemic exposure. More than 90% of a dose is recovered in the urine, approximately two-thirds as eslicarbazepine and one-third as its glucuronide conjugate. A reduction in dosage is recommended in patients with moderate and severe renal impairment. Dosage adjustment is not necessary in patients with mild or moderate hepatic impairment. The drug has not been studied in patients with severe hepatic impairment, and its use in these patients is not recommended.

Eslicarbazepine should not be used with oxcarbazepine because of the extent to which their actions overlap and the potential for an excessive response. Enzyme-inducing AEDs such as phenytoin, phenobarbital, and primidone may reduce the plasma concentration of eslicarbazepine and necessitate an increased dosage of the latter agent. Although carbamazepine may also reduce the plasma concentration of eslicarbazepine, concurrent use of the two agents may increase the risk of certain adverse events (e.g., dizziness). Therefore, the dosage of both agents should be individualized based on the response and tolerability of the patient. The concomitant use of eslicarbazepine and phenytoin should also be closely monitored as the plasma concentration and action of the latter agent may be increased.
Eslicarbazepine may inhibit the CYP2C19 metabolic pathway and induce the CYP3A4 pathway, and the concurrent use of medications that are substrates for these pathways should be closely monitored. The new drug has been reported to reduce plasma concentrations of ethinyl estradiol and levonorgestrel, and women of reproductive potential should use additional or alternative nonhormonal contraception.

The recommended initial dosage of eslicarbazepine is 400 mg once a day. After one week, the dosage should be increased to 800 mg once a day, which is the recommended maintenance dosage. Among those patients who tolerate the 800 mg daily dosage for at least a week, some may benefit from a further increase to the maximum recommended maintenance dosage of 1200 mg once a day, although there is a higher incidence of adverse events with this dosage.

In patients with moderate or severe renal impairment, treatment should be initiated with a dosage of 200 mg once a day. After two weeks, the dosage should be increased to 400 mg once a day, which is the recommended maintenance dosage. Some patients may benefit from an increase to the maximum recommended maintenance dosage of 600 mg once a day.

If treatment with eslicarbazepine is to be discontinued, the dosage should be reduced gradually to avoid abrupt discontinuation and minimize the risk of increased seizure frequency and status epilepticus.

Eslicarbazepine acetate tablets are supplied in 200 mg, 400 mg, 600 mg, and 800 mg potencies.

**Anti-inflammatory agent**

Of the approximately 8 million Americans who experience psoriasis, up to 40% also develop psoriatic arthritis that is most often characterized by joint pain, stiffness, and swelling. A nonsteroidal anti-inflammatory drug is often used as the initial treatment for mild forms of psoriatic arthritis. Medications used for the treatment of moderate to severe disease include the disease-modifying antirheumatic drugs (DMARDs; e.g., methotrexate), corticosteroids, tumor necrosis factor (TNF) blockers (i.e., adalimumab [Humira], certolizumab [Cimzia], etanercept [Enbrel], golimumab [Simponi], infliximab [Remicade]), and the interleukin-12/interleukin-23 inhibitor ustekinumab (Stelara).

**Apremilast** (Otezla—Celgene) is a phosphodiesterase-4 (PDE4) inhibitor that is indicated for oral use in the treatment of adult patients with active psoriatic arthritis. PDE4 mediates the conversion of cyclic adenosine monophosphate (cAMP) to AMP that can contribute to the occurrence of inflammation. By inhibiting PDE4, apremilast increases intracellular cAMP concentrations, resulting in a reduced inflammatory response. Roflumilast (Daliresp) is another PDE4 inhibitor available for therapeutic use, but it is indicated to reduce the risk of chronic obstructive pulmonary disease (COPD) exacerbations in patients with severe COPD.

The effectiveness of apremilast was evaluated in three placebo-controlled studies in patients with active psoriatic arthritis despite prior or current DMARD therapy. Some patients had been previously treated with a biologic, including TNF blockers. The primary endpoint was the percentage of patients achieving an American College of Rheumatology (ACR) 20 response (representing at least a 20% improvement from baseline in most measures of disease activity) at week 16. Patients whose tender and swollen joint counts had not improved at least 20% by week 16 were considered non-responders.

In the three studies, the percentages of patients treated with apremilast who achieved an ACR 20 response were 38%, 32%, and 41%, compared with 19%, 19%, and 18%, respectively, in patients receiving placebo. Patients treated with the new drug experienced improvement in each of the seven components of the ACR evaluation (e.g., number of tender joints, number of swollen joints, patient assessment of pain). The percentages of patients achieving an ACR 50 response or ACR 70 response at 16 weeks were 16%, 11%, and 15%, and 4%, 1%, and 4%, respectively. However, these results were not statistically significantly different from those with placebo.

Apremilast has not been directly compared with other medications in clinical studies. However, the results of studies of the individual agents suggest that the new drug is less effective than the TNF blockers and ustekinumab in improving ACR responses. Apremilast is also being evaluated for the treatment of patients with psoriasis and ankylosing spondylitis. Although these are not labeled indications at the present time, it is likely to soon be approved for the treatment of psoriasis.

The adverse events reported most often in the clinical studies of apremilast are nausea (9%), diarrhea (8%), and headache (6%). Dosage titration is recommended to reduce the gastrointestinal symptoms associated with initial therapy. One percent of the patients reported depression or depressed mood, and suicidal ideation or behavior was observed in 0.2%. Whether or not apremilast should be used in patients with a history of these experiences should be carefully evaluated. If the drug is prescribed, these patients, as well as their family members and/or caregivers, should be advised of the importance of being alert for the emergence or worsening of such responses.

Ten percent of the patients treated with apremilast experienced a weight decrease between 5% and 10% of body weight, compared with 3% of those receiving placebo. Patients should have their weight monitored regularly and, in the event that excessive weight loss occurs, consideration should be given to discontinuing treatment.

Apremilast is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. A pregnancy registry has been established (877–311–8972) to monitor outcomes in women exposed to the drug during pregnancy. It is not known whether the drug is excreted in human milk, and caution must be exercised when the drug is used by a nursing woman. The effectiveness and safety of apremilast in

www.pharmacist.com OCTOBER 2014 • Pharmacy Today 73
patients less than 18 years of age have not been established.

Because it is effective following oral administration, apremilast has an advantage over TNF blockers and ustekinumab that are administered parenterally. Following administration, the drug has an absolute bioavailability of 73%. Administration with food does not alter the extent of its absorption. Apremilast is extensively metabolized, primarily via the CYP3A4 metabolic pathway with subsequent glucuronidation and hydrolysis. Approximately 58% and 39% of a dose is recovered in the urine and feces, respectively, predominantly in the form of metabolites. The dosage of apremilast should be reduced in patients with severe renal impairment.

Concurrent use of rifampin, a strong cytochrome P450 enzyme inducer, resulted in a reduction of systemic exposure to apremilast, which may result in a loss of efficacy. Accordingly, the concurrent use of apremilast with enzyme inducers such as rifampin, carbamazepine, phenobarbital, and phenytoin is not recommended.

The dosage of apremilast is titrated over the first 5 days of treatment. On day 1, a dose of 10 mg is administered in the morning; on day 2, 10 mg is administered in both the morning and evening; on day 3, 10 mg is administered in the morning and 20 mg in the evening; on day 4, 20 mg is administered in both the morning and evening; on day 5, 20 mg is administered in the morning and 30 mg in the evening; and on day 6 and thereafter, the recommended maintenance dosage of 30 mg in both the morning and evening is administered. In patients with severe renal impairment (creatinine clearance less than 30 mL per minute), the morning doses should be administered, but not the evening doses, with a recommended maintenance dosage of 30 mg once a day.

Apremilast film-coated tablets are supplied in 10 mg, 20 mg, and 30 mg potencies. A two-week starter pack includes tablets in three potencies for the dosage titration period plus additional 30 mg tablets. For maintenance use, a package is available that contains two blister cards that each contain 14 of the 30 mg tablets.

**Antidiabetic agent**

**Dapagliflozin propanediol** (Farxiga—Bristol-Myers Squibb; AstraZeneca) is the second drug in a new class of orally administered antidiabetic agents designated as sodium-glucose cotransporter 2 (SGLT2) inhibitors, joining canagliflozin (Invokana). SGLT2 is expressed in the proximal renal tubules and is responsible for the reabsorption of the majority of glucose filtered by the kidneys. By inhibiting SGLT2, canagliflozin and dapagliflozin reduce the reabsorption of filtered glucose, increase urinary glucose excretion, and reduce blood glucose and glycosylated hemoglobin (hemoglobin A1c [HbA1c]) concentrations.

Like canagliflozin, dapagliflozin is specifically indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Its effectiveness has been demonstrated in studies in which it was used as monotherapy or in combination regimens with metformin, glipizide, glimepiride, pioglitazone, sitagliptin (Januvia), or insulin.

The use of dapagliflozin resulted in reductions in HbA1c and fasting plasma glucose (FPG) concentrations and, in many patients, weight reduction. In a placebo-controlled study, the percentage of patients achieving an HbA1c of less than 7% was 44% and 51% in patients receiving daily doses of 5 mg and 10 mg of dapagliflozin, respectively, compared with 32% of those receiving placebo. The use of dapagliflozin in combination with other antidiabetic agents resulted in greater reductions in HbA1c and FPG concentrations. Patients treated with regimens that included dapagliflozin typically lost an average of 1–3 kg of body weight over a 24-week period, whereas those who were treated with other antidiabetic agents usually either lost less weight or experienced weight gain.

The use of dapagliflozin is not recommended in patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis. There have been infrequent reports (0.3%) of serious hypersensitivity reactions in patients treated with dapagliflozin, and the use of the new drug is contraindicated in patients with a history of such an experience.

As with canagliflozin, dapagliflozin increases serum creatinine concentrations and decreases estimated glomerular filtration rate (eGFR). Older patients and those with impaired renal function are more susceptible to associated risks. The use of dapagliflozin is contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m²), end-stage renal disease, or patients on dialysis. Renal function should be evaluated before initiating treatment and periodically thereafter. Treatment should not be initiated in patients with an eGFR less than 60 mL/min/1.73 m², and if the eGFR is persistently less than this value during treatment, the drug should be discontinued.

Dapagliflozin causes intravascular volume contraction that may result in symptomatic hypotension. Volume status should be assessed, and corrected if necessary, in older patients, in patients with impaired renal function or low systemic blood pressure, and in patients treated with a diuretic.

Although dapagliflozin does not cause hypoglycemia, it can increase the risk of hypoglycemia when used in combination with insulin or an insulin secretagogue (e.g., sulfonylurea). Therefore, a lower dosage of the latter agent may be necessary when such combination regimens are used.

The most commonly experienced adverse events in the clinical studies of dapagliflozin (and the incidence in patients treated with a dosage of 10 mg daily) include female genital mycotic infections (7%; e.g., vulvovaginal candidiasis), nasopharyngitis (6%), urinary tract infections (4%), increased urination (4%), back pain (4%), male genital mycotic infections (3%; e.g., balanitis), nausea (3%), and dyslipidemia (3%; e.g., increased LDL-C).

In the 22 studies in which dapagliflozin has been evaluated,
nosine monophosphate (cGMP), producing smooth muscle stimulation. NO then activates the enzyme guanylate cyclase.

The erectile mechanism of erection of the penis involves release of tadalafil (Cialis), and vardenafil (Levitra, Staxyn). The physiological mechanism of erection of the penis involves release of nitric oxide (NO), which relaxes smooth muscle in the corpus cavernosum and allows increased blood flow into the penis and erection. PDE5 is responsible for the degradation of cGMP in the corpus cavernosum, and the inhibition of PDE5 enhances the effect of NO. Because sexual stimulation is required to initiate the local release of NO, the inhibition of PDE5 has no effect in the absence of sexual stimulation.

Each of the PDE5 inhibitors has been demonstrated to be significantly more effective than placebo in the treatment of erectile dysfunction in clinical trials. Men who have experienced benefit with the use of these agents include those with diseases or clinical situations associated with a higher frequency of erectile dysfunction (e.g., diabetes, radical prostatectomy). The PDE5 inhibitors have not been directly compared with each other, but they appear to be similar in efficacy. Preference for one of these agents sometimes will be based on its onset of action or duration of action. Tadalafil has a longer duration of action and more dosage/treatment options, which may be an advantage in permitting greater spontaneity in facilitating intercourse. However, it has a slower onset of action than the other agents. Avanafil appears to have a faster onset of action than the other agents and most patients can take the new drug approximately 15 minutes before sexual activity. Sildenafil and vardenafil are usually taken approximately 60 minutes before sexual activity.

The PDE5 inhibitors are used on an as-needed basis for the treatment of erectile dysfunction. However, tadalafil is also used in a lower dosage once a day without regard to timing of sexual activity. Tadalafil is also indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH), as well as for the treatment of both BPH and erectile dysfunction. These latter situations are not labeled indications for avanafil at the present time.

The risks and adverse events associated with the use of avanafil are generally similar to those for sildenafil, tadalafil, and vardenafil. As with the other PDE5 inhibitors, the use of avanafil with any form of an organic nitrate (e.g., nitroglycerin), either regularly and/or intermittently, is contraindicated because it may potentiate the hypotensive effects of nitrates. If a nitrate is considered necessary in a life-threatening situation, it should be administered under close medical supervision with appropriate hemodynamic monitoring.

The PDE5 inhibitors exhibit a vasodilating action and can also increase the blood pressure-lowering effect of alpha-adrenergic blocking agents (e.g., tamsulosin), as well as other antihypertensive agents. In patients who are stabilized on alpha-blocker therapy, the use of a PDE5 inhibitor should be initiated at the lowest dose (i.e., 5 mg of avanafil). In patients already using a PDE5 inhibitor, treatment with an alpha-blocker should be initiated at the lowest dose. Alcohol also has a vasodilating action and patients should be advised that...
substantial consumption of alcoholic beverages (greater than 3 units [e.g., glasses of wine, shots of whiskey]) in combination with avanafil may increase the potential for orthostatic signs and symptoms (e.g., decrease in standing blood pressure, dizziness).

Because of a potential for cardiac risk during sexual activity in patients with pre-existing cardiovascular disease, avanafil should not be used in men for whom sexual activity is inadvisable because of their underlying cardiovascular status. The clinical studies of avanafil did not include patients who had suffered an acute myocardial infarction, stroke, life-threatening arrhythmia, or coronary revascularization during the last 6 months, patients with resting hypotension (blood pressure less than 90/50 mm Hg) or hypertension (greater than 170/100 mm Hg), or patients with unstable angina.

The use of the PDE5 inhibitors has been infrequently associated with prolonged erection greater than 4 hours and priapism (painful erections greater than 6 hours in duration). If an erection persists for longer than 4 hours, the patient should seek immediate medical assistance. Avanafil and the other PDE5 inhibitors should be used with caution in patients who have conditions that may predispose them to priapism (e.g., sickle cell anemia, multiple myeloma) or who have anatomical deformation of the penis (e.g., Peyronie’s disease).

There have been rare occurrences of a sudden loss of vision in one or both eyes in patients treated with a PDE5 inhibitor, and this may be a sign of nonarteritic anterior ischemic optic neuropathy (NAION) that has been reported in temporal association with the use of these agents. Patients who experience such a reaction should discontinue use of the drug and seek medical attention. The PDE5 inhibitors have also been associated with a sudden decrease or loss of hearing, which may be accompanied by tinnitus or dizziness. If this occurs, the drug should be discontinued and medical attention sought.

The most commonly experienced adverse events (and their incidence with a dose of 100 mg) in the clinical studies of avanafil include headache (7%), flushing (4%), nasal congestion (3%), nasopharyngitis (3%), and back pain (2%). Hypersensitivity reactions (pruritus, eyelid swelling) have been reported with avanafil, and it is contraindicated in patients with a known hypersensitivity to any component of the tablet formulation. The safety of the new drug in patients with bleeding disorders or active peptic ulceration is not known.

Following oral administration, avanafil is rapidly absorbed and the maximum concentration is usually attained in 30–45 minutes when administered in the fasting state. Although consumption of a high-fat meal may reduce the rate of absorption, it may be administered without regard to food. It is extensively metabolized in the liver, primarily via the CYP3A4 pathway, and its metabolites have weak or no pharmacologic activity. Avanafil is excreted as metabolites predominantly in the feces (approximately 62% of a dose) and to a lesser extent in the urine (approximately 21%).

Dosage adjustment is not necessary in patients with mild to moderate hepatic impairment or mild to moderate renal impairment. However, it has not been studied in patients with severe hepatic or renal impairment and is not recommended for use in patients with these conditions.

The action of avanafil is increased by the concurrent use of a CYP3A4 inhibitor. Its use should be avoided in patients being treated with a strong CYP3A4 inhibitor (e.g., clarithromycin, itraconazole, ritonavir). In patients being treated with a moderate CYP3A4 inhibitor (e.g., diltiazem, fluconazole, verapamil), the maximum recommended dose of avanafil is 50 mg, and it should not be used more than once every 24 hours.

The recommended starting dose of avanafil is 100 mg, taken as needed approximately 15 minutes before sexual activity. Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or reduced to 50 mg. The maximum recommended dosing frequency is once a day.

Avanafil tablets are supplied in 50 mg, 100 mg, and 200 mg potencies.

**Agent for menopause-associated conditions**

There are approximately 33 million women in the United States between the ages of 45 and 59, and the average age of menopause in this country is 51. Menopause is associated with reduced functioning of the ovaries during aging that results in lower concentrations of estrogens and other hormones. The reduction of estrogen concentrations is often accompanied by moderate-to-severe vasomotor symptoms (hot flashes) and followed by bone loss and an increased risk of osteoporosis. Approximately 50% of American women 50 years and older have low bone mass that places them at higher risk for osteoporosis.

Estrogens have been used for more than 60 years as a hormonal replacement therapy to manage menopausal symptoms. Although estrogens are effective in reducing menopausal symptoms, when used alone they increase the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. To reduce this risk of endometrial problems, a progestin has been used in combination with an estrogen.

A combination of **conjugated estrogens and bazedoxifene acetate** (Duavee—Pfizer) has recently been approved for the treatment of menopause-associated conditions. Products containing conjugated estrogens (e.g., Premarin) have been available for decades, but bazedoxifene is a new therapeutic agent. Bazedoxifene is an estrogen agonist/antagonist, also designated as a selective estrogen receptor modulator (SERM), that activates estrogen receptors in some tissues while inhibiting estrogen activity in others (e.g., the uterus). The combination product is the first to be approved that includes an estrogen agonist/antagonist instead of a progestin to reduce the risk of endometrial hyperplasia associated with
the use of estrogen alone for the treatment of menopause-associated conditions.

The combination of conjugated estrogens and bazedoxifene is specifically indicated in women with a uterus for the treatment of moderate-to-severe vasomotor symptoms associated with menopause and for prevention of postmenopausal osteoporosis. As with other products containing estrogen, conjugated estrogens/bazedoxifene should be used for the shortest duration consistent with treatment goals and risks for the individual woman. When treatment is considered solely for the prevention of postmenopausal osteoporosis, the new product should only be used in women at significant risk of osteoporosis and non-estrogen medication should be carefully considered.

The effectiveness of conjugated estrogens/bazedoxifene in the treatment of vasomotor symptoms was demonstrated in a placebo-controlled study in which the new product significantly reduced the number and severity of hot flashes. In studies in which the new product was evaluated for the prevention of postmenopausal osteoporosis, it significantly increased lumbar spine bone mineral density and total hip bone mineral density.

Bazedoxifene joins several other agents that are classified as estrogen agonist/antagonists and that are indicated for use in postmenopausal women.Raloxifene (Evista) is indicated for the treatment and prevention of osteoporosis and for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis or who are at high risk of invasive breast cancer. Ospemifene (Osphena) was marketed in 2013 for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause.

The most commonly experienced adverse events in the placebo-controlled trials of conjugated estrogens/bazedoxifene include muscle spasms (8%), nausea (8%), diarrhea (8%), dyspepsia (7%), upper abdominal pain (7%), oropharyngeal pain (7%), neck pain (5%), and dizziness (5%).

The contraindications and other risks associated with the use of the conjugated estrogens/bazedoxifene combination include potential problems that could result from the use of estrogen alone (i.e., the conjugated estrogens component of the combination product). The new product is contraindicated in patients with undiagnosed abnormal uterine bleeding; known, suspected, or past history of breast cancer; known or suspected estrogen-dependent neoplasia; active or past history of venous or arterial thromboembolism; known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorder; known hepatic impairment or disease; and those who are hypersensitive to any component of the product. The product is classified in Pregnancy Category X and is contraindicated in women who are pregnant or who may become pregnant, as well as in nursing mothers.

Studies that have evaluated estrogen-alone treatment have reported increased risks of stroke and deep vein thrombosis (DVT), as well as probable dementia in postmenopausal women 65 years of age and older, and these concerns are included as boxed warnings in the labeling for the conjugated estrogens/bazedoxifene combination. There are also boxed warnings in the labeling that estrogen therapy should not be used for the prevention of cardiovascular disease or dementia, and that there is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogen.

Estrogen therapy has also been associated with an increased risk of cardiovascular disorders, hypertriglyceridemia, gallbladder disease, visual abnormalities, and hypothyroidism. Thyroid function should be monitored, as women who are being treated with thyroid replacement therapy who are also receiving estrogens may require increased doses of thyroid replacement therapy. Women for whom the conjugated estrogens/bazedoxifene combination is prescribed should not take additional estrogens or estrogen agonist/antagonists, or progestins.

Following oral administration conjugated estrogens are well-absorbed, but the absolute bioavailability of bazedoxifene is approximately 6%. Estrogens are partially metabolized via the CYP3A4 pathway, whereas bazedoxifene undergoes metabolism by uridine diphosphate glucuronosyltransferase (UGT) enzymes in the intestinal tract and liver. The conjugated estrogen components are excreted in the urine, and bazedoxifene is primarily eliminated via biliary excretion, followed by elimination in the feces. The product has not been studied in women with renal impairment or women older than 75 years, and its use is not recommended in these patients.

The concurrent use of a CYP3A4 inhibitor (e.g., clarithromycin, itraconazole, grapefruit juice) may increase the exposure of conjugated estrogens, and CYP3A4 inducers (e.g., carbamazepine, rifampin, St. John’s wort) may reduce plasma concentrations of estrogens. Inducers of UGTs (e.g., carbamazepine, rifampin) may increase the metabolism of bazedoxifene and reduce its exposure.

Duavee tablets each contain 0.45 mg of conjugated estrogens and a quantity of bazedoxifene acetate equivalent to 20 mg of bazedoxifene. The recommended dosage is one tablet daily. In women who are taking the product for the prevention of postmenopausal osteoporosis, supplemental calcium and/or vitamin D should be taken if daily intake is not adequate.
CPE Assessment

Instructions: This exam must be taken online; please see “CPE information” for further instructions. The online system will present these questions in random order to help reinforce the learning opportunity. There is only one correct answer to each question.

1. Which of the following drug classification pairings is correct?
   a. umeclidinium : long-acting beta-2-adrenergic agonist
   b. dapagliflozin : dipeptidyl peptidase-4 inhibitor
   c. bazedoxifene : estrogen agonist/antagonist
   d. eslicarbazepine : phosphodiesterase-4 inhibitor

2. Which of the following agents is administered twice a day?
   a. apremilast
   b. perampanel
   c. eslicarbazepine
   d. dapagliflozin

3. Which of the following agents has a boxed warning in its labeling regarding serious psychiatric reactions?
   a. bazedoxifene
   b. apremilast
   c. avanafil
   d. perampanel

4. With the use of which of the following agents is vulvovaginal candidiasis the most commonly experienced adverse event?
   a. apremilast
   b. dapagliflozin
   c. bazedoxifene

5. Which of the following agents is classified as a controlled substance?
   a. eslicarbazepine
   b. apremilast
   c. perampanel
   d. bazedoxifene

6. Which of the following agents is contraindicated in patients being treated with an organic nitrate?
   a. umeclidinium
   b. avanafil
   c. apremilast

7. Which of the following statements is correct regarding the umeclidinium/vilanterol combination?
   a. It is administered by nasal inhalation.
   b. It is indicated for the maintenance treatment of asthma.
   c. Its indications include the treatment of acute bronchospasm.
   d. It is the first combination formulation to include a long-acting muscarinic antagonist and a long-acting beta-2-adrenergic agonist.

8. Which of the following statements is correct regarding the umeclidinium/vilanterol combination?
   a. Concurrent use with medications with anticholinergic activity should be avoided.
   b. The dosage should be reduced in patients with impaired renal function.
   c. It is administered twice a day.
   d. The product is supplied in capsules that are placed in an inhalation device that pierces the capsule to release the medication.

9. Which of the following statements is correct regarding perampanel?
   a. It is classified as a glutamate receptor agonist.
   b. It is indicated for use as monotherapy in the treatment of Lennox-Gastaut syndrome.
   c. It is indicated as adjunctive therapy for the treatment of partial-onset seizures.
   d. Fatigue is the most common adverse event associated with its use.

CPE information

To obtain 2.0 contact hours (0.2 CEUs) of CPE credit for this activity, you must complete the online Assessment, Learning Evaluation, and Activity Evaluation. All exam questions are randomized and may not appear in the same order as printed. Credit will be awarded upon achieving a passing grade of 70% or better. You will have two opportunities to successfully complete the CPE Assessment. Please note that you will not be permitted to submit answers a third time. Pharmacists who successfully complete this activity by October 1, 2017, can receive a Statement of Credit, which will be stored on “My Training Page” and on CPE Monitor for future viewing/printing. The current policy of the APhA Education Department is to not release the correct answers to any of our CPE tests. This policy is intended to maintain the integrity of the CPE activity and the test.

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10. Which of the following statements is correct regarding perampanel?
   a. It is teratogenic and is classified in Pregnancy Category X.
   b. It should be administered with food to increase its bioavailability.
   c. It should be used in a higher dosage in patients who are also being treated with an enzyme-inducing antiepileptic drug.
   d. Its use is contraindicated in patients with hepatic impairment.

11. Which of the following statements is correct regarding eslicarbazepine?
   a. It is a prodrug that is rapidly metabolized to carbamazepine.
   b. It is used in combination regimens that also include oxcarbazepine.
   c. It has been approved for use in adults and children 6 years and older.
   d. Dizziness is the adverse event most often associated with its use.

12. Which of the following statements is correct regarding apremilast?
   a. It may reduce the concentration of hormonal contraceptives, and women of reproductive potential should use additional or alternative nonhormonal contraception.
   b. It must be administered apart from food.
   c. A reduction in dosage is recommended in patients with moderate or severe hepatic impairment.
   d. Treatment is initiated with a loading dose that is reduced after one week to the maintenance dosage.

13. Which of the following statements is correct regarding dapagliflozin?
   a. It reduces the reabsorption of filtered glucose and increases urinary glucose excretion.
   b. It has been demonstrated to be more effective than canagliflozin in reducing plasma glucose concentrations.
   c. It reduces serum creatinine concentrations and renal function should be regularly monitored.
   d. Its use is commonly associated with the occurrence of hypoglycemia.

16. Which of the following statements is correct regarding dapagliflozin?
   a. It is available as a single agent and in a combination product with metformin.
   b. There were infrequent reports of bladder cancer in the clinical studies and it should not be used in patients with active bladder cancer.
   c. It must be administered apart from food.
   d. It is excreted in unchanged form in the urine.

17. Which of the following statements is correct regarding avanafil?
   a. Its labeled indications include erectile dysfunction and benign prostatic hyperplasia.
   b. It is a prodrug that is converted to sildenafil following administration.
   c. It has a longer duration of action than tadalafl.
   d. It is administered approximately 15 minutes before sexual activity.

18. Which of the following statements is correct regarding avanafil?
   a. Its use is contraindicated in patients treated with an alpha-adrenergic blocking agent.
   b. It is less likely than vardenafil and tadalafil to cause priapism.
   c. Its use should be avoided in patients being treated with a strong CYP3A4 inhibitor.
   d. Visual changes are the most common adverse events associated with its use.

19. Which of the following statements is correct regarding bazedoxifene?
   a. It has been designated as a selective estrogen receptor modulator.
   b. It is indicated for the prevention and treatment of postmenopausal osteoporosis.
   c. Its labeled indications include dyspareunia due to menopause.
   d. When used in women with postmenopausal osteoporosis, vitamin C supplements should also be taken.