New therapeutic agents marketed in the first half of 2011: Part 1

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Abstract

Objective: To provide information regarding the most important properties of the new therapeutic agents marketed in the first half of 2011.

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

Study selection: By the author.

Data extraction: By the author.

Data synthesis: 14 new therapeutic agents were marketed in the United States during the first half of 2011, 7 of which are reviewed in this article (part 1 of a two-part series): ceftaroline fosamil, azilsartan medoxomil, belimumab, lurasidone hydrochloride, linagliptin, and alcaftadine. Indications and information on dosage and administration for these agents are reviewed, as are the most important pharmacokinetic properties, adverse events, drug interactions, and other precautions. Practical considerations for the use of the new agents are also discussed. When possible, the properties of the new drugs are compared with those of older drugs marketed for the same indications.

Conclusion: Only two of the seven new drugs considered in part 1 of this series have mechanisms of action and/or other properties that distinguish them in an important manner from previously marketed drugs. Belimumab is the first new drug to be approved for the treatment of systemic lupus erythematosus since 1955. It inhibits the survival of abnormal B cells that may be responsible, in part, for symptoms and signs associated with lupus. Ceftaroline is the first cephalosporin to be approved for an infection (acute bacterial skin and skin structure infections) caused by methicillin-resistant isolates of *Staphylococcus aureus*. An understanding of the properties of the new medications is important for the pharmacist to effectively counsel patients about their use and to serve as a valuable source of information for other health professionals regarding these drugs.

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

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Learning objectives

At the conclusion of this knowledge-based activity, the pharmacist will be able to:
- Identify the new therapeutic agents marketed during January to June 2011 and explain their appropriate use.
- Identify the indications and the most important adverse events and other risks of each of the new therapeutic agents.
- State the route of administration for each new drug and the important considerations regarding dosage and administration.
- Demonstrate appropriate patient counseling regarding the use of the new medications and the precautions to be observed.

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Preassessment questions
Before participating in the activity, test your knowledge by answering the following questions. These questions also will be part of the CPE exam.

1. Which of the following agents is administered every 12 hours?
   a. Linagliptin
   b. Azilsartan
   c. Ceftaroline
   d. Vilazodone

2. Which of the following agents should be administered with food?
   a. Lurasidone
   b. Azilsartan
   c. Linagliptin
   d. Belimumab

3. With the use of which of the following agents is it recommended that the dosage be titrated in two additional steps following the initiation of treatment?
   a. Linagliptin
   b. Lurasidone
   c. Azilsartan
   d. Vilazodone

Antibiotic

Ceftaroline fosamil (Teflaro—Forest) is a water-soluble prodrug that is converted to its active form, ceftaroline, during intravenous infusion. Ceftaroline is a cephalosporin that, like its predecessors in this class of antibiotics, exhibits a bactericidal action by inhibiting penicillin-binding proteins and inhibiting bacterial cell wall synthesis. It is active against numerous Gram-positive and Gram-negative bacteria and is the first cephalosporin to be approved for an infection caused by methicillin-resistant isolates of *Staphylococcus aureus* (MRSA).

Ceftaroline is specifically indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) caused by susceptible isolates of *S. aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca* and for treatment of community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of *Streptococcus pneumoniae* (including cases with concurrent bacteremia). *S. aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *K. pneumoniae*, *K. oxytoca*, and *E. coli*.

The demonstration of effectiveness of ceftaroline in the studies of patients with ABSSSIs used cessation of spread of the lesion and absence of fever on day 3 as the primary endpoint. The new drug was compared with vancomycin (e.g., Vancocin) plus aztreonam (e.g., Azactam), and the two regimens were considered comparable in effectiveness. Studies of ceftaroline in patients with CABP used improvement in signs and symptoms of pneumonia on day 4 as the primary endpoint. The new drug was compared with ceftiraxone (Rocephin), and the two agents were considered comparable in effectiveness. The effectiveness of ceftaroline against MRSA was not evaluated in patients with CABP because few of the patients had pneumonia caused by MRSA and the comparator drug (ceftiraxone) is not effective against MRSA.

As with the other cephalosporins, as well as the other classes of beta-lactam antibiotics (i.e., penicillins, carbapenems), ceftaroline has been reported to cause hypersensitivity/anaphylactic reactions. The new drug is contraindicated in patients with known serious hypersensitivity to any of the cephalosporins and, because of the potential for cross-sensitivity with other beta-lactam antibiotics, caution must be exercised if it is to be considered for use in a patient known to be allergic to a penicillin or carbapenem.

Almost all systemic antibacterial agents, including ceftaroline, have been reported to cause *Clostridium difficile*-associated diarrhea (CDAD) that may range in severity from mild diarrhea to fatal colitis. CDAD should be considered in all patients who experience diarrhea following antibiotic use, including the period of time following completion of antibiotic therapy, because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents.

Seroconversion from a negative to a positive direct Coombs’ test result occurred in 11% of patients treated with ceftaroline in the clinical studies compared with 4% of those receiving the comparator antibiotics. In the studies in which ceftaroline was compared with ceftiraxone, seroconversion occurred in 10% and 5% of the patients, respectively. Adverse events associated with hemolytic anemia were not reported in any of the patients in the studies. However, if anemia develops during or after treatment with ceftaroline, hemolytic anemia should be considered.

Other adverse events reported in the clinical studies of ceftaroline included diarrhea (5%), nausea (4%), and rash (3%). Treatment was discontinued because of adverse events in 3% of patients compared with 4% of the patients treated with the comparator antibiotics. With each of the antibiotics studied, hypersensitivity was the most common adverse event that resulted in discontinuation of treatment.

Ceftaroline is classified in Pregnancy Category B. Its effectiveness and safety in pediatric patients have not been established.

Ceftaroline and its metabolites are primarily eliminated by the kidneys, predominantly by glomerular filtration. Dosage adjustment is not necessary in patients with mild renal impairment but is recommended in patients with moderate or severe renal impairment. The activity of ceftaroline is not likely to be significantly affected by hepatic impairment.

The recommended dosage of ceftaroline is 600 mg every 12 hours by intravenous infusion administered over a period of 1 hour. The duration of therapy should be guided by the severity and site of the infection, as well as the patient’s progress, but is usually 5–7 days for the treatment of CABP and 5–14 days for the treatment of ABSSSIs. The dosage should be reduced to
400 mg every 12 hours in patients with moderate renal impairment (creatinine clearance between 30 and 50 mL/minute), 300 mg every 12 hours in patients with severe renal impairment (creatinine clearance between 15 and 30 mL/minute), and 200 mg every 12 hours in patients with end-stage renal disease, including hemodialysis. Because ceftaroline is hemodialyzable, it should be administered after hemodialysis on hemodialysis days.

Ceftaroline fosamil is supplied in powder form in single-use vials containing 400 and 600 mg of the drug. The vials should be stored in a refrigerator. The contents of a vial should be constituted with 20 mL of Sterile Water for Injection, and this solution should be further diluted in a volume of at least 250 mL of 0.9% Sodium Chloride Injection, 0.45% Sodium Chloride Injection, 5% Dextrose Injection, 2.5% Dextrose Injection, or Lactated Ringer’s Injection. The diluted solution in the infusion bag should be administered within 6 hours when stored at room temperature or within 24 hours when stored under refrigeration.

Antihypertensive agent
Azilsartan medoxomil (Edarbi—Takeda) is the eighth angiotensin II receptor blocker (ARB) to be marketed in the United States, joining candesartan cilexetil (Atacand), eprosartan (Teveten), irbesartan (Avapro), losartan (e.g., Cozaar), olmesartan medoxomil (Benicar), telmisartan (Micardis), and valsartan (Diovan). The ARBs directly block the binding of the potent vasoconstrictor angiotensin II to its receptor sites, thereby causing a reduction in blood pressure. All of the ARBs selectively block the AT1 subtype angiotensin II receptors.

The form of azilsartan that is used in its tablet formulation is the potassium salt of azilsartan medoxomil, which also is known as azilsartan kamedoxomil. Like candesartan cilexetil and olmesartan medoxomil, azilsartan medoxomil is a prodrug, and the new agent is hydrolyzed to azilsartan in the gastrointestinal tract during absorption.

As with the other ARBs, azilsartan is indicated for the treatment of hypertension and may be used alone or in combination with other antihypertensive agents, most often a diuretic. In studies in which it was compared with olmesartan and valsartan, azilsartan was more effective in lowering 24-hour blood pressure. The reduction in the 24-hour mean systolic blood pressure was 14.3 mm Hg with azilsartan (80 mg once a day), compared with reductions of 11.7 and 10 mm Hg with olmesartan (40 mg/day) and valsartan (320 mg/day), respectively. As with the other ARBs, azilsartan was less effective in lowering blood pressure in black patients.

In addition to hypertension, certain of the ARBs also have been approved for additional indications (e.g., valsartan for the treatment of heart failure in patients who are intolerant of angiotensin-converting enzyme inhibitors [ACEIs], candesartan and losartan for the treatment of diabetic nephropathy in patients with type 2 diabetes and hypertension). However, these are not labeled indications for azilsartan at the present time.

Like the other ARBs, azilsartan is well tolerated, with diarrhea (2%) being the most common adverse event reported in the clinical studies. Although the ARBs are not likely to cause symptomatic hypotension, caution should be exercised when azilsartan is used in volume- or salt-depleted patients (e.g., those using diuretics), and the use of a lower dosage should be considered. The ARBs have a potential to cause changes in renal function, and azilsartan should be used with caution in patients who are at greatest risk of such a response (e.g., those with preexisting renal impairment or renal artery stenosis). The concurrent use of a nonsteroidal anti-inflammatory drug (NSAID) may result in a deterioration of renal function in at-risk patients. In addition, the antihypertensive effect of azilsartan may be reduced by NSAIDs.
Neonatal morbidity and death are risks if either an ARB or ACEI is used during the second or third trimesters of pregnancy, and this is addressed in a boxed warning in the labeling for these agents. Like the other agents, azilsartan is classified in Pregnancy Categories C (first trimester) and D (second and third trimesters). If a woman treated with one of these agents becomes pregnant, treatment should be discontinued as soon as possible.

Whether azilsartan is excreted in human milk is unknown; therefore, in nursing mothers, a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of azilsartan in pediatric patients have not been established.

Following oral administration, azilsartan medoxomil is rapidly hydrolyzed to azilsartan, the absolute bioavailability of which is approximately 60%. It is metabolized to two primary metabolites, primarily via the cytochrome P450 (CYP)2C9 pathway, but the metabolites do not contribute to the activity of the drug. Approximately 55% of the drug is recovered in the feces and approximately 40% in the urine. Dosage adjustment is not considered necessary in patients with impaired renal function or in patients with mild or moderate hepatic impairment. The new drug has not been studied in patients with severe hepatic impairment.

The recommended dosage of azilsartan is 80 mg once a day, with or without food. In patients who are also being treated with a diuretic in a high dosage, consideration should be given to initiating treatment with azilsartan in a dosage of 40 mg once a day.

Azilsartan kamedoxomil is supplied in tablets in quantities representing the equivalent of 40 and 80 mg of azilsartan medoxomil. The tablets should be dispensed and stored in the original container to protect the drug from light and moisture and should not be repackaged. A combination formulation that also includes a diuretic is under development.

**Agent for systemic lupus erythematosus**

Systemic lupus erythematosus (SLE; lupus) is a serious and potentially fatal autoimmune disease that attacks healthy tissues, including the joints, skin, kidneys, lungs, heart, and brain. The symptoms that are most commonly experienced (flare) are joint pain and inflammation, light sensitivity, fever, fatigue, chest pain, and hair loss. More than 300,000 Americans are afflicted with lupus. It most often affects women and usually develops between 15 and 44 years of age. The incidence in black women is approximately three times higher than in white women.

Standard therapies for lupus have included nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids (e.g., prednisone), immunosuppressives (e.g., azathioprine, methotrexate, mycophenolate), and antimalarials (hydroxychloroquine [Plaquenil]). However, in some patients, these agents have been of limited effectiveness and serious complications are experienced.

**Belimumab** (Benlysta—Human Genome Sciences; GlaxoSmithKline) is the first new drug to be approved for the treatment of lupus since 1955, when hydroxychloroquine and corticosteroids were approved for this disease. It is thought that abnormal B cells may be responsible, in part, for symptoms and complications associated with lupus and that these cells may contribute to the formation of autoantibodies. Belimumab is a human monoclonal antibody produced by recombinant DNA technology that is specific for soluble human B lymphocyte stimulator protein (BLYS), a B-cell survival factor. As a BLYS-specific inhibitor, the new drug blocks the binding of soluble BLYS to its receptors on B-cells. This action inhibits the survival of B-cells, including autoreactive B-cells, and reduces the differentiation of B-cells into immunoglobulin-producing plasma cells.

Belimumab is administered intravenously and is specifically indicated for the treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. In the clinical studies, patients received belimumab plus standard therapy or placebo plus standard therapy. Patients receiving belimumab experienced less disease activity than those receiving placebo. Some patients treated with belimumab had a reduced likelihood of severe flares, and in some, it was possible to reduce the dosage of the corticosteroid that was included as part of their standard therapy; however, the data were insufficient to establish these responses as definitive benefits of the new drug. Black patients who participated in the studies did not appear to benefit from belimumab treatment, although the numbers of these patients were not large enough to reach definite conclusions and additional studies will be conducted in black patient populations.

Patients with severe active lupus nephritis and severe active central nervous system lupus were excluded from the clinical trials, as were patients who were being treated with other biologics or intravenous cyclophosphamide. Therefore, the use of belimumab is not recommended in these situations.

Hypersensitivity reactions and infusion reactions have been experienced by some patients treated with belimumab but at an incidence not much greater than in patients receiving placebo. In the clinical studies, hypersensitivity reactions were reported in 13% and 11% of those receiving belimumab and placebo, respectively, and anaphylaxis was observed in 0.6% and 0.4%, respectively. The use of the new agent is contraindicated in patients who have previously experienced anaphylaxis to the drug. Infusion reactions (e.g., headache, nausea, skin reactions) were reported in 17% of patients treated with belimumab and 15% of those receiving placebo. Because of the overlap in signs and symptoms, distinguishing between hypersensitivity reactions and infusion reactions was not always possible. Some patients were provided with premedication, but data were insufficient to determine whether premedication diminished the frequency or severity of hypersensitivity or infusion reactions.

As with other agents with immunosuppressive activity, a risk of serious infections exists with use of belimumab. Infections were reported in 71% and 67% of the patients receiving belimumab and placebo, respectively, in the clinical trials, and infections resulting in death occurred in 0.3% and 0.1% of patients, respectively. Treatment with belimumab should not be initiated in patients receiving therapy for a chronic in-
fection, and in patients undergoing treatment with belimumab who develop a new infection, interruption of therapy should be considered. During the controlled period of clinical trials, more deaths were reported (e.g., from infections, cardiovascular disease, suicide) with belimumab than with placebo.

Because belimumab may interfere with the response to immunizations, live vaccines should not be given for 30 days before or concurrently with the new drug.

Psychiatric adverse events (e.g., depression, anxiety) were reported more frequently in patients treated with belimumab (16%) in the clinical trials than those who were receiving placebo (12%). Although most of the patients who experienced these events had a history of these problems and were being treated with psychoactive medications, patients treated with belimumab should be instructed to report new or worsening depression, suicidal thoughts, or other mood changes.

The most frequently experienced adverse events in the clinical studies with belimumab included nausea (15%), diarrhea (12%), pyrexia (10%), nasopharyngitis (9%), bronchitis (9%), insomnia (7%), pain in extremity (6%), depression (5%), migraine (5%), and pharyngitis (5%). Although anti-belimumab antibodies were detected in only a small percentage of patients, a potential exists for the development of neutralizing antibodies.

Belimumab is classified in Pregnancy Category C, and women of childbearing potential should use adequate contraception during treatment with the drug and for at least 4 months following the final treatment. For women who are pregnant during the time period in which they are being treated with belimumab, enrollment in the Pregnancy Registry (877-681-6296) is encouraged. Whether belimumab is excreted in human milk is not known, and a decision should be made to discontinue nursing or not use the drug. The effectiveness and safety of belimumab in pediatric patients have not been evaluated.

Belimumab is administered via intravenous infusion over a period of 1 hour and must not be administered as an intravenous push or bolus. The recommended dosage is 10 mg/kg at 2-week intervals for the first three doses and at 4-week intervals thereafter. If a patient develops an infusion reaction, the infusion may be interrupted or the rate slowed. If a serious hypersensitivity reaction is experienced, the infusion must be discontinued immediately.

Belimumab lyophilized powder is supplied in single-use vials containing 120 and 400 mg of the drug. The vials should be stored in a refrigerator. When preparing a dose of the drug, the vial should be removed from the refrigerator and allowed to stand for 10 to 15 minutes to reach room temperature. Vials containing 120 mg of the drug should be reconstituted with 1.5 mL Sterile Water for Injection, and the vials containing 400 mg should be reconstituted with 4.8 mL Sterile Water for Injection. The reconstituted solutions contain belimumab in a concentration of 80 mg/mL. The sterile water should be directed toward the side of the vial to minimize foaming, and the vial should be gently swirled (but not shaken) for 60 seconds. The vial should be gently swirled for 60 seconds every 5 minutes until the powder is dissolved (usually within 15 minutes). If a mechanical reconstitution device (swirler) is used to reconstitute the drug, it should not exceed 500 rpm and the vial should not be swirled for longer than 30 minutes. The reconstituted formulation should be diluted to 250 mL in 0.9% Sodium Chloride Injection. A volume of diluent equal to the volume of reconstituted solution required for the patient’s dose should be withdrawn from the infusion bag or bottle of 0.9% Sodium Chloride Injection. The required volume of the reconstituted solution of the drug then should be added to the infusion bag or bottle, which then should be gently inverted to mix the solution. The total time from reconstitution of belimumab to completion of infusion should not exceed 8 hours.

Dextrose solutions are incompatible with belimumab and should not be used for either reconstituting or diluting the drug.

Antipsychotic agent

Lurasidone hydrochloride (Latuda—Sunovion) is an atypical antipsychotic agent that is classified as a benzisothiazol derivative. Its properties are most similar to those of risperidone (e.g., Risperdal, paliperidone [Invega], iloperidone [Fanapt], and ziprasidone [Geodon]). Other atypical antipsychotic agents include aripiprazole (Abilify), asenapine (Saphris), clozapine (e.g., Clozaril), olanzapine (Zyprexa), and quetiapine (Seroquel). Lurasidone is indicated for the treatment of patients with schizophrenia, and its action is thought to be mediated through a combination of central dopamine type 2 (D2) and serotonin type 2 (5HT2a) receptor antagonism.

The effectiveness of lurasidone was demonstrated in four short-term (6-week) placebo-controlled studies in adult patients with schizophrenia. In three of the four studies, each of the dosage regimens of lurasidone evaluated was superior to placebo, whereas in one study in which dosages of 40, 80, or 120 mg/day were used, only the 80 mg/day dosage was superior to placebo. In one study, one group of patients received olanzapine as an active control. Olanzapine also was demonstrated to be superior to placebo, but the study was not powered to compare lurasidone with olanzapine.

Many of the other atypical antipsychotic agents also are indicated for other psychiatric disorders (e.g., bipolar disorder) in addition to schizophrenia. However, schizophrenia is the only labeled indication for lurasidone at the present time.

Most of the warnings and precautions associated with lurasidone are similar to those of the other atypical antipsychotic agents. The labeling for all of these agents includes a boxed warning regarding increased mortality in elderly patients with dementia-related psychosis, as well as the statement that these agents have not been approved for treating patients with dementia-related psychosis. Other shared warnings and precautions include the potential for cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis, neuroleptic malignant syndrome, tardive dyskinesia, hyperprolactinemia, hyperglycemia/diabetes, weight gain, orthostatic hypotension/syncope, seizures, cognitive and motor impairment, dysphagia, problems associated with body temperature regulation, and leukopenia, neutropenia, and agranulocytosis. The possibility of suicide is inherent in psychiatric
illness, and these drugs should be prescribed in the smallest quantities consistent with good patient management to reduce the possibility of overdosage.

The adverse events experienced most frequently in the clinical studies with lurasidone include somnolence (22%), akathisia (15%), nausea (12%), parkinsonism (11%), agitation (6%), anxiety (6%), and dystonia (5%). Compared with most of the other atypical antipsychotic agents, lurasidone appears less likely to cause metabolic changes such as diabetes and weight gain but may be more likely to cause somnolence/sedation. Unlike ziprasidone and iloperidone, lurasidone has not been associated with significant prolongation of the QT interval of the electrocardiogram.

Lurasidone is classified in Pregnancy Category B. Whether it is excreted in human milk is unknown, and it should only be used in a nursing mother if the anticipated benefit justifies the risk to the child. The effectiveness and safety of lurasidone in pediatric patients have not been established.

Following oral administration, less than 20% of a dose of lurasidone is absorbed. The peak serum concentration and bioavailability of the drug are increased when it is administered with food. Patients in the clinical studies were instructed to take the medication with food, and it is recommended that doses be administered with food (at least 350 calories).

Lurasidone is metabolized primarily via the CYP3A4 pathway. Although two of the metabolites are active, most of the activity is caused by the parent drug. The activity of lurasidone may be increased considerably by the concurrent use of a strong CYP3A4 inhibitor (e.g., ketoconazole) and reduced considerably by a strong CYP3A4 inducer (e.g., rifampin). Accordingly the concomitant use of lurasidone with one of these agents is contraindicated. Because of the potential for additive central nervous system (CNS)-depressant effects, caution must be exercised when lurasidone is used in patients taking other CNS depressants, including alcoholic beverages.

Approximately 80% of a dose of lurasidone is recovered in the feces and 10% in the urine. The bioavailability of the drug is increased in patients with renal or hepatic impairment.

The recommended initial dosage of lurasidone is 40 mg once a day with food, and the maximum recommended dosage is 80 mg once a day. A dosage of 120 mg/day has not been demonstrated to provide added benefit, but a dose-related increase was seen in certain adverse events. The dosage should not exceed 40 mg a day in patients with moderate or severe renal impairment, moderate or severe hepatic impairment, or in patients treated concurrently with a moderate CYP3A4 inhibitor (e.g., diltiazem).

Lurasidone hydrochloride tablets are supplied in 40 and 80 mg potencies.

**Antidepressant**

**Vilazodone hydrochloride** (Viibryd—Forest) is a selective serotonin reuptake inhibitor (SSRI) with properties that are most similar to those of citalopram, escitalopram (Lexapro), fluoxetine, paroxetine, and sertraline. The new drug differs from its predecessors by also acting as a partial agonist at serotonergic 5-HT_1A receptors; however, whether this partial agonist action contributes to the antidepressant effect provided by vilazodone is not known.

Vilazodone is indicated for the treatment of adult patients with major depressive disorder, and its effectiveness has been demonstrated in two 8-week placebo-controlled trials. It has not been directly compared with other antidepressants in clinical studies, and there are no data that suggest that it is more effective than other SSRIs in the treatment of depression. Some patients who have not experienced an adequate response with one (or more) SSRIs have experienced benefit with the use of another SSRI, and the potential exists for vilazodone to be effective in some patients who have not responded adequately to another SSRI. None of the agents in this class have been demonstrated to be consistently more effective than the others.

In addition to the treatment of depression, most of the previously marketed SSRIs (with citalopram being the exception), also have been approved for certain other disorders such as generalized anxiety disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, social anxiety disorder, and premenstrual dysphoric disorder. However, these are not labeled indications for vilazodone at the present time.

The drug-related problems, warnings, and precautions associated with the use of vilazodone are generally similar to those for the other SSRIs. The labeling for each of these agents includes a boxed warning regarding the increased risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (aged 18–24 years). Depression itself is associated with an increased risk of suicide, and all patients being treated with an SSRI or other antidepressant should be closely observed for clinical worsening, suicidality, or unusual changes in behavior.

Because of the risk of serious and even fatal interactions, vilazodone is contraindicated in patients being treated with a monoamine oxidase inhibitor (MAOI) or who have taken a MAOI within the preceding 14 days. In patients who are treated with vilazodone first, an interval of at least 14 days should elapse following discontinuation of vilazodone before starting treatment with an MAOI.

Potentially life-threatening serotonin syndrome or neurolptic malignant syndrome (NMS)-like reactions have been reported with the use of the SSRIs when used alone, and the risk of such reactions is increased by the concomitant use of other agents having serotonergic activity (e.g., serotonin–noradrenaline reuptake inhibitors [e.g., venlafaxine], triptans, tramadol) or antidopaminergic activity (e.g., antipsychotic agents). In patients in whom the use of such combination therapy is clinically warranted, treatment must be closely monitored, particularly when treatment is initiated and when dosages are increased. If symptoms suggestive of serotonin syndrome or NMS occur, treatment should be discontinued immediately. The concurrent use of vilazodone with a serotonin precursor such as tryptophan is not recommended.

The SSRIs have been associated with the occurrence of seizures, activation of mania/hypomania, hypotension, and ab-
normal bleeding. The risk of bleeding is increased in patients who are also being treated with warfarin or another anticoagulant, aspirin, or a nonsteroidal anti-inflammatory drug.

The adverse events reported most frequently in the clinical studies with vilazodone included diarrhea (28%), nausea (23%), vomiting (5%), dizziness (9%), and insomnia (6%). Some patients have experienced sexual dysfunction (e.g., decreased libido, erectile dysfunction). Vilazodone was not observed to cause a significant change in body weight during the 8-week period of the clinical studies. However, data are insufficient to determine whether increases in weight occur over longer periods of treatment, such as have been associated with the continued use of other SSRIs.

Because vilazodone may cause central nervous system (CNS) effects (e.g., dizziness), patients should be cautioned about engaging in activities such as driving and operating machinery until they have determined how the medication may affect their alertness and judgment. Caution also must be exercised when other CNS-active drugs are used concurrently, and patients should be advised to avoid drinking alcoholic beverages while taking vilazodone.

Vilazodone is classified in Pregnancy Category C and should be used in a pregnant or nursing woman only if the anticipated benefit justifies the risk to the fetus/child. The effectiveness and safety of vilazodone in patients younger than 18 years have not been evaluated. Certain of the other SSRIs have been approved for the treatment of depression in younger patients. For example, in addition to its indication for the treatment of adult patients, escitalopram also is approved for the treatment of depression in adolescent patients aged 12 to 17 years.

Following oral administration, the absolute bioavailability of vilazodone is 72% when the drug is administered with food. Administration with food (high fat or light meal) increases bioavailability substantially, and administration without food can result in inadequate drug concentrations and may reduce effectiveness. Vilazodone is extensively metabolized through cytochrome P450 (CYP; primarily CYP3A4) and non-CYP pathways. Only a small fraction of the drug is eliminated in unchanged form. Adjustment of dosage is not necessary in patients with renal impairment or in patients with mild or moderate hepatic impairment. The drug has not been studied in patients with severe hepatic impairment.

The concurrent use of a strong CYP3A4 inhibitor (e.g., clarithromycin, ketoconazole) can increase the plasma concentration and activity of vilazodone, and reducing the dosage of the latter agent by one-half is recommended. The concurrent use of a CYP3A4 inducer has the potential to reduce the concentration of vilazodone, although the extent to which its activity may be changed has not been evaluated. Vilazodone has been shown in in vitro studies to be a moderate inhibitor of CYP2C19 and CYP2D6, and concurrent use with other medications that are substrates for these metabolic pathways should be monitored closely.

Vilazodone should be administered with food, and the recommended maintenance dosage is 40 mg once a day. Treatment should be initiated with a dosage of 10 mg once a day for 7 days, followed by 20 mg once a day for an additional 7 days, and then an increase to 40 mg once a day. The dosage should be reduced to 20 mg once a day in patients who also are being treated with a strong inhibitor of CYP3A4. If a moderate inhibitor of CYP3A4 (e.g., erythromycin) is used concurrently, the dosage should be reduced to 20 mg once a day in patients who experience intolerable adverse events. Dosage adjustment is not considered necessary when vilazodone is used concomitantly with a mild CYP3A4 inhibitor (e.g., cimetidine).

Adverse events have been reported when treatment with antidepressants with serotonergic activity is discontinued. Whenever possible, the dosage should be gradually reduced, and not abruptly discontinued.

Vilazodone hydrochloride immediate-release, film-coated tablets are supplied in 10, 20, and 40 mg potencies.

Antidiabetic agent

The incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinoptropic polypeptide (GIP) are involved in the physiologic regulation of glucose homeostasis. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells, and GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output. The incretin hormones are secreted at a low level throughout the day, and in larger amounts in the presence of elevated glucose concentrations (e.g., following meals).

In 2005, exenatide (Byetta) was marketed as the first agent for the treatment of diabetes that acts by increasing the action of incretins. Liraglutide (Victoza), an agent that acts similarly, was marketed in 2010. However, both of these agents must be administered by injection (subcutaneously). In 2006, sitagliptin (Januvia) was marketed as the first of a new class of antidiabetic agents that can be administered orally to increase the actions of incretins. The incretins are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). Sitagliptin is a DPP-4 inhibitor that slows the inactivation of incretins, thereby increasing and prolonging their action. A related agent, saxagliptin (Onglyza) was marketed in 2009.

Linagliptin (Tradjenta—Boehringer Ingelheim; Lilly) is the third DPP-4 inhibitor, and its properties and use are very similar to those of sitagliptin and saxagliptin. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. It is not effective in treating patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

The effectiveness of linagliptin was demonstrated in placebo-controlled studies in which it was evaluated as monotherapy and in combination with metformin, glimepiride, and pioglitazone (Actos). The new agent provided significant improvements in glycosylated hemoglobin (A1C), fasting plasma glucose, and 2-hour postprandial glucose. Linagliptin reduced A1C by up to 0.7% compared with placebo when used as monotherapy and by a slightly smaller increment (0.5–0.6%) when used in combination with other antidiabetic agents. The new
drug has not been directly compared with sitagliptin or saxagliptin in clinical studies.

Like its predecessors, linagliptin is well tolerated, with nasopharyngitis (6%) being the adverse event most commonly reported in the clinical studies. Hypersensitivity reactions with the use of linagliptin have been reported infrequently; however, this possibility is not specifically identified as a warning in its labeling as it is in the labeling for sitagliptin.

Subsequent to its initial marketing, the labeling for sitagliptin was revised based on postmarketing reports to include a warning about a risk of acute pancreatitis. Although the labeling for saxagliptin and linagliptin do not include such a specific warning, these agents also should be considered to have the potential to cause this problem.

The DPP-4 inhibitors do not cause hypoglycemia and are not likely to cause hypoglycemia when used in combination with metformin. However, their concurrent use with an antidiabetic agent with a known potential to cause hypoglycemia (e.g., a sulfonylurea) should be monitored closely, and a lower dosage of the latter agent may be required.

Linagliptin is classified in Pregnancy Category B. Whether the drug is excreted in human milk is not known, and caution should be exercised if it is administered to a nursing woman. The effectiveness and safety of linagliptin in pediatric patients have not been established.

Linagliptin is a P-glycoprotein substrate. Although it has been reported to inhibit P-glycoprotein-mediated transport of digoxin at high concentrations, the results of studies suggest that it is not likely to interact with other P-glycoprotein substrates at therapeutic concentrations. Inducers of P-glycoprotein or CYP3A4, such as rifampin, reduce exposure to linagliptin to subtherapeutic concentrations, and the use of an alternative to linagliptin is strongly recommended. Sitagliptin is not likely to interact with other medications via pharmacokinetic mechanisms, whereas the activity of saxagliptin is increased by the concurrent use of a strong CYP3A4/5 inhibitor (e.g., clarithromycin, ketoconazole). Although linagliptin has been reported in in vitro studies to be a weak to moderate inhibitor of CYP3A4, clinically important interactions with medications that are CYP3A4 substrates appear unlikely.

Linagliptin may be administered with or without food, and its absolute bioavailability is approximately 30%. Although a small fraction of the drug that is absorbed is metabolized to a pharmacologically inactive metabolite, approximately 90% of a dose is excreted unchanged, primarily via the enterohepatic system.

The recommended dosage of linagliptin is 5 mg once a day. Only approximately 5% of a dose is eliminated via the urine, and it is not necessary to reduce the dosage in patients with impaired renal function. This is an advantage over both sitagliptin and saxagliptin, for which the dosage should be reduced in patients with moderate or severe renal impairment or end-stage renal disease.

Linagliptin tablets are supplied in a 5-mg potency. Both sitagliptin and saxagliptin are also available in combination formulations with metformin (Janumet and Kombiglyze XR, respectively). However, at the present time, linagliptin is not available in a similar combination product.

**Agent for allergic conjunctivitis**

Allergic conjunctivitis is the most common type of ocular allergy, with itching being the most prominent symptom, although redness, tearing, burning, and lid edema also may occur. Both oral and ophthalmic antihistamines are effective in relieving symptoms, but the ophthalmic antihistamines have a more rapid onset of action and are less likely to cause systemic adverse events. **Alcaftadine** (Lastacaft—Allergan) is the sixth ophthalmic antihistamine that also acts as an inhibitor of the release of histamine from mast cells (mast cell stabilizer), joining azelastine (Optivar), bepotastine (Bepreve), epinastine (Elestat), ketotifen (e.g., Alaway, Zaditor), and olopatadine (Patanol, Pataday). Following administration into the eyes, alcaftadine is metabolized to its active carboxylic acid metabolite.

Alcaftadine is specifically indicated for ophthalmic use for the prevention of itching associated with allergic conjunctivitis. It was more effective than its vehicle in preventing ocular itching in patients with allergic conjunctivitis induced by an ocular allergen challenge. However, studies in which it was directly compared with other antihistamine/mast cell stabilizers are very limited, and there are no data to suggest that it is more effective than the other agents.

Most patients tolerated alcaftadine well, and the most frequently experienced ocular adverse events included eye irritation, burning, and/or stinging upon instillation, eye redness, and eye pruritus, each of which occurred in less than 4% of patients. The most common nonocular adverse events, each of which was reported in less than 3% of patients, included nasopharyngitis, headache, and influenza.

Alcaftadine is classified in Pregnancy Category B, whereas the other antihistamine/mast cell stabilizers are in Pregnancy Category C. Its effectiveness and safety in children younger than 2 years of age have not been established.

Alcaftadine is supplied in an ophthalmic solution that contains the drug in a concentration of 0.25%. The recommended dosage is one drop in each eye once daily, a regimen that is more convenient, with one exception, than those for the other antihistamine/mast cell stabilizers that are administered twice a day. The one exception is a newer higher concentration (0.2%) formulation of olopatadine (Pataday) that is also administered just once a day.

Like many other ophthalmic solution formulations, alcaftadine ophthalmic solution contains benzalkonium chloride as a preservative, and this agent may be absorbed by soft contact lenses. Contact lenses should be removed before instilling the solution and may be reinserted 10 minutes after administration. Patients should be advised not to wear a contact lens if their eye is red, and alcaftadine should not be used to treat contact lens–related irritation.

Like most of the other antihistamine/mast cell stabilizers used in ophthalmic formulations for allergic conjunctivitis, alcaftadine requires a prescription. However, an ophthalmic solution formulation of ketotifen is available without a prescription for the temporary relief of itchy eyes.
CPE exam

Instructions: The assessment test for this activity must be taken online; please see “CPE information” below for further instructions. There is only one correct answer to each question. This CPE activity will be available online at www.pharmacist.com no later than October 31, 2011.

1. Which of the following agents is administered every 12 hours?
   a. Linagliptin
   b. Azilsartan
   c. Cefaroline
   d. Vilazodone

2. Which of the following agents should be administered with food?
   a. Lurasidone
   b. Azilsartan
   c. Linagliptin
   d. Bellimunab

3. With the use of which of the following agents is it recommended that the dosage be titrated in two additional steps following the initiation of treatment?
   a. Linagliptin
   b. Lurasidone
   c. Azilsartan
   d. Vilazodone

4. With the use of which of the following agents is it recommended that women of childbearing potential use adequate contraception during treatment and for at least 4 months following treatment?
   a. Cefaroline
   b. Bellimunab
   c. Azilsartan
   d. Vilazodone

5. The clinical benefit of which of the following agents is attributed to its serotonergic activity?
   a. Lurasidone
   b. Linagliptin
   c. Azilsartan
   d. Vilazodone

6. Which of the following statements is correct regarding cefaroline?
   a. Elevations of alanine aminotransferase and aspartate aminotransferase are the most common laboratory abnormalities associated with its use.
   b. It is primarily eliminated in the feces, and dosage adjustment is not necessary in patients with renal impairment.
   c. It is administered by intravenous infusion over a period of 1 hour.
   d. Hemolytic anemia is the adverse event that most often resulted in the discontinuation of treatment in the clinical studies.

7. Which of the following statements is correct regarding cefaroline?
   a. Elevations of alanine aminotransferase and aspartate aminotransferase are the most common laboratory abnormalities associated with its use.
   b. It is primarily eliminated in the feces, and dosage adjustment is not necessary in patients with renal impairment.
   c. It is administered by intravenous infusion over a period of 1 hour.
   d. Hemolytic anemia is the adverse event that most often resulted in the discontinuation of treatment in the clinical studies.

8. Which of the following statements is correct regarding azilsartan?
   a. It is classified as an angiotensin-converting enzyme inhibitor.
   b. Its labeled indications include the treatment of hypertension and congestive heart failure.
   c. In studies in which it was compared with valsartan, it was less effective than valsartan in lowering 24-hour blood pressure.
   d. Its blood pressure–lowering action may be reduced by the concurrent use of a nonsteroidal anti-inflammatory drug.

9. Which of the following statements is correct regarding azilsartan?
   a. Dosage adjustment is not necessary in patients with impaired renal function.
   b. It should not be used during pregnancy, and the highest risk of harm to the fetus occurs in the first trimester.
   c. It must be administered apart from food to attain optimal absorption.
   d. It is supplied as a single agent and in a combination formulation with hydrochlorothiazide.

CPE information

To obtain 2.0 contact hours of CPE credit (0.2 CEUs) for this activity, complete and submit the CPE exam online at www.pharmacist.com/education. A Statement of Credit will be awarded for a passing grade of 70% or better. You will have two opportunities to successfully complete the CPE exam. Pharmacists who successfully complete this activity before October 15, 2014, can receive credit.

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3. Successfully complete the CPE exam and evaluation form to gain immediate access to your documentation of credit.

Live step-by-step assistance is available Monday through Friday 8:30 am to 5:00 pm ET at APhA Member Services at 800-237-APhA (2742) or by e-mailing InfoCenter@pharmacist.com.
10. Which of the following statements is correct regarding belimumab?
   a. It acts by increasing the activity of B lymphocyte stimulator protein thereby restoring normal B cell function.
   b. It is used in conjunction with standard therapy in patients with active, autoantibody-positive, systemic lupus erythematosus.
   c. It was most effective in the clinical studies in patients with severe active lupus nephritis.
   d. It is often used with intravenous cyclophosphamide to provide a greater benefit than is attained with either agent alone.

11. Which of the following statements is correct regarding belimumab?
   a. It is classified as an immunostimulant.
   b. It is administered subcutaneously.
   c. It is administered at 2-week intervals for the first three doses and at 4-week intervals thereafter.
   d. The lyophilized powder containing the drug should be reconstituted with 5% Dextrose Injection.

12. Which of the following statements is correct regarding lurasidone?
   a. Its effectiveness is attributed to an antagonist action at certain dopamine and serotonin receptors.
   b. It has been approved for the treatment of schizophrenia and bipolar disorder.
   c. It appears to be more effective than other antipsychotic agents in the treatment of patients with dementia-related psychosis.
   d. It has been demonstrated in clinical studies to be more effective than olanzapine.

13. Which of the following statements is correct regarding lurasidone?
   a. Insomnia is the adverse event that was reported most often in the clinical studies.
   b. Prolongation of the QT interval of the electrocardiogram is an important precaution to be observed with its use.
   c. It is not pharmacologically active itself but it is rapidly converted to active metabolites following administration.
   d. It is metabolized primarily via the cytochrome P450 (CYP)3A4 pathway.

14. Which of the following statements is correct regarding lurasidone?
   a. Its concurrent use with a strong CYP3A4 inhibitor is contraindicated.
   b. It is almost completely absorbed following oral administration.
   c. Most of a dose is eliminated in the urine.
   d. Its use is contraindicated in patients with hepatic impairment.

15. Which of the following statements is correct regarding vilazodone?
   a. It is classified as a serotonin and norepinephrine reuptake inhibitor.
   b. It has been approved for the treatment of patients with major depressive disorder and generalized anxiety disorder.
   c. It has been demonstrated in clinical studies to be more effective than escitalopram.
   d. Concurrent use or use within 14 days of a monoamine oxidase inhibitor is contraindicated.

16. Which of the following statements is correct regarding vilazodone?
   a. It has been approved for use in adult and adolescent patients.
   b. Diarrhea is the adverse event that was reported most often in the clinical studies.
   c. Weight gain was experienced by many patients in the clinical studies.
   d. Myalgia is a common adverse event and the concurrent use with a statin should be avoided.

17. Which of the following statements is correct regarding vilazodone?
   a. It has been approved for use in adult and adolescent patients.
   b. Diarrhea is the adverse event that was reported most often in the clinical studies.
   c. Weight gain was experienced by many patients in the clinical studies.
   d. Myalgia is a common adverse event and the concurrent use with a statin should be avoided.

18. Which of the following statements is correct regarding linagliptin?
   a. It is metabolized to only a limited extent and is eliminated primarily in its unchanged form.
   b. Its dosage should be reduced in patients with impaired renal function.
   c. It is a moderate inhibitor of the CYP2C19 and CYP2D6 metabolic pathways.
   d. It has a short duration of action and is supplied in a controlled-release formulation.

19. Which of the following statements is correct regarding linagliptin?
   a. Concurrent use with rifampin should be avoided.
   b. It is extensively metabolized via glucuronidation pathways.
   c. The dosage should be reduced in patients with impaired renal function.
   d. It is supplied as a single agent and in a combination formulation with metformin.

20. Which of the following statements is correct regarding alcaftadine?
   a. It exhibits both antihistamine and decongestant actions.
   b. It is approved for use in adult and adolescent patients but not for use in children younger than 12 years.
   c. It is administered once a day.
   d. It is available without a prescription.