New therapeutic agents marketed in the second half of 2009: Part 1
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Abstract

Objective: To provide information regarding the most important properties of the new therapeutic agents marketed in the second half of 2009.

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 second half of 2009, 7 of which are reviewed in this article (part 1 of a two-part series): prasugrel hydrochloride, dronedarone hydrochloride, asenapine, iloperidone, saxagliptin hydrochloride, ustekinumab, and bepotastine besilate. 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: Most of the new drugs discussed in this article have properties and uses that are very similar to those of older drugs. However, one of these new drugs, ustekinumab, has a unique mechanism of action and is more effective than other drugs for the treatment of moderate to severe plaque psoriasis. Prasugrel and dronedarone have benefits for selected patients, but the other new agents do not have considerable advantages compared with previously marketed agents. An understanding of the properties of these 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.


Learning objectives
At the conclusion of this program, the pharmacist will be able to:

- Identify the new therapeutic agents marketed during July to December 2009 and explain their appropriate use.
- Describe 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.

ACPE Activity Type: Knowledge-Based
Antiplatelet agent

Acute coronary syndrome (ACS), which includes unstable angina and myocardial infarction (MI), affects approximately 1.5 million Americans each year. Many of these individuals are candidates for percutaneous coronary intervention (PCI: angioplasty), a procedure in which a balloon device is used to open coronary arteries that are narrowed and clogged by atherosclerotic plaque. Often, a stent is inserted into the blood vessel to help keep the artery open following the procedure. Although the benefit of these procedures is well documented, aggregation of platelets around the procedure site is possible, potentially resulting in the formation of clots that can lead to heart attack, stroke, and death. Clopidogrel (Plavix) has been widely used to reduce the risk of clot formation following PCI.

Prasugrel hydrochloride (Effient—Daiichi Sankyo; Lilly) is a thienopyridine derivative that is structurally and pharmacologically related to clopidogrel and ticlopidine (e.g., Ticlid). Like these agents, prasugrel is a prodrug and is converted to an active metabolite that inhibits platelet activation and aggregation by binding to the P2Y₁₂ class of adenosine 5’-diphosphate receptors on platelets. Following oral administration, prasugrel undergoes rapid hydrolysis and subsequent conversion to its active metabolite by a CYP-mediated step. Clopidogrel undergoes biotransformation via two competing metabolic pathways, with the major pathway producing an inactive metabolite and the minor pathway producing the active metabolite after it goes through two sequential CYP-dependent steps.

Prasugrel is specifically indicated to reduce the rate of thrombotic cardiovascular events (including stent thrombosis) in patients with ACS who are to be managed with PCI, including patients with unstable angina or non-ST-elevation MI (NSTEMI) and patients with ST-elevation MI when managed with primary or delayed PCI. The effectiveness of the new drug was demonstrated in studies in which it was used in conjunction with aspirin and compared with a regimen of clopidogrel plus aspirin. The primary outcome measure was the composite of cardiovascular death, nonfatal MI, and nonfatal stroke. When compared with the clopidogrel/aspirin regimen, the prasugrel/aspirin regimen provided a 19% relative risk reduction with respect to the composite endpoint, although the benefit was almost entirely attributable to a reduction in nonfatal MI. Fewer stent-related clots (i.e., stent thrombosis) were observed in patients treated with prasugrel/aspirin, with a relative risk reduction of approximately 50%.

The greater effectiveness of prasugrel reported in these studies must be considered in the context of a greater risk of bleeding, including life-threatening and fatal bleeding. One analysis of the reduction in cardiovascular events and the risk of bleeding has reported an overall benefit favoring prasugrel compared with clopidogrel. For every 1,000 patients treated with prasugrel, as compared with clopidogrel, 23 fewer patients had nonfatal heart attacks and 6 more had major bleeding events.

Different opinions exist regarding the results of the studies in which prasugrel was compared with clopidogrel. Some have proposed that if a lower dosage of prasugrel had been used in the clinical studies, there might be little or no difference in the efficacy of the two agents and the risk of bleeding. In the labeling for prasugrel, an “alternative explanation” is included for the differences reported in the comparison of the two drugs. The labeling notes that the pharmacokinetic properties of the active metabolite of clopidogrel were affected by the CYP2C19 genotype and that approximately 30% of whites are reduced metabolizers. It is further noted that a proton pump inhibitor is often used by patients with ACS and that certain of these agents (i.e., omeprazole [e.g., Prilosec]) inhibit CYP2C19, thereby decreasing the formation of the active metabolite of clopidogrel. The extent to which these two factors may have influenced the comparison of clopidogrel and prasugrel was not evaluated.

The indications for prasugrel are more limited than those for clopidogrel. The indications for clopidogrel also include use in patients with NSTEMI who are to be managed medically (as well as in those to be managed with PCI) and patients who are to be managed with coronary artery bypass graft (CABG) surgery. Clopidogrel is also indicated for reducing atherothrombotic events in patients with a history of recent MI, recent stroke, or established peripheral arterial disease. However, these are not labeled indications for prasugrel at the present time.

The risk of bleeding is the most important concern with the use of prasugrel and is the subject of a boxed warning in its labeling. The new drug is contraindicated in patients with active pathological bleeding (e.g., peptic ulcer, intracranial hemorrhage) and in patients with a history of previous transient ischemic attack (TIA) or stroke. In the largest comparative study, patients with a history of TIA or ischemic stroke had a higher incidence of stroke when treated with prasugrel (6.5%) than with clopidogrel (1.2%). The use of clopidogrel is not contraindicated in patients with a history of TIA or stroke and, indeed, is indicated for use in selected patients with a history of recent stroke.

Because of an increased risk of bleeding, treatment with prasugrel should not be initiated in patients who are likely to undergo urgent CABG surgery. If possible, use of the new drug should be discontinued at least 7 days before any surgery. Additional risk factors for bleeding with the use of prasugrel include body weight less than 60 kg, propensity to bleed (e.g., recent trauma), concomitant use of medications that increase the risk of bleeding (e.g., warfarin, heparin, chronic use of nonsteroidal anti-inflammatory drugs), and age of 75 years or older. The use of prasugrel is generally not recommended in patients 75 years or older, except in high-risk situations (patients with a history of diabetes or a history of previous MI) in which the benefit of the drug appears to be greater and its use may be considered. If bleeding occurs during treatment with prasugrel, an attempt should be made to manage the bleeding without discontinuing the drug because discontinuing treatment may increase the risk of subsequent cardiovascular events. Patients should be informed of the importance of adherence with the dosage instructions and to avoid lapses in therapy. Prasugrel and the other thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7–10 days); therefore, withholding a dose

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Dronedarone itself is a moderate inhibitor of CYP3A and -2D6 and may interact with medications that are substrates of these metabolic pathways. It may increase the action of drugs, such as certain statins (e.g., simvastatin [e.g., Zocor]), sirolimus (Rapamune), tacrolimus (Prograf), and CYP2D6 substrates, such as certain selective serotonin reuptake inhibitors (e.g., fluoxetine [e.g., Prozac]).

Dronedarone also has the potential to inhibit P-glycoprotein transport and has been reported to increase digoxin exposure by 2.5-fold. In addition, digoxin may potentiate the electrophysiologic effects of dronedarone, and the need for digoxin should be reconsidered. If digoxin treatment is continued, the dosage should be reduced by one-half.

Dronedarone may interact with calcium channel blockers (e.g., diltiazem, verapamil) and beta-blockers (e.g., propranolol, metoprolol) via multiple mechanisms. Calcium channel blockers exhibit a depressant effect on the sinus and AV nodes and could potentiate dronedarone’s effects on conduction. Diltiazem and verapamil are moderate CYP3A inhibitors and increase dronedarone exposure by up to 1.7-fold, and dronedarone increases the exposure of calcium channel blockers by up to 1.5-fold. The concurrent use of a beta-blocker with dronedarone increases the possibility of bradycardia, and the exposure of the beta-blockers that are CYP2D6 substrates (e.g., propranolol, metoprolol) is increased by dronedarone. When a calcium channel blocker or beta-blocker is to be used in a patient being treated with dronedarone, they should be used initially in a low dosage that is increased only after electrocardiogram verification of good tolerability.

Dronedarone film-coated tablets are supplied in a 400-mg potency. The only recommended dosage is 400 mg twice a day with the morning meal and the evening meal.

**Antipsychotic agents**

**Asenapine** (Saphris—Schering) and **iloperidone** (Fanapt—Novartis) are new atypical antipsychotic agents that join an already large class of these drugs that includes aripiprazole (Abilify), clozapine (e.g., Clozaril), olanzapine (Zyprexa), quetiapine (Seroquel), ziprasidone (Geodon), and risperidone (e.g., Risperdal) and its active metabolite paliperidone (Invega). Both new drugs have been approved for the acute treatment of schizophrenia in adults, and asenapine has also been approved for the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. The labeled indications for asenapine and iloperidone are more limited than those of their predecessors, with which long-term experience and additional studies have resulted in an extension of the indications for which they were initially approved. Although much remains to be learned regarding the mechanisms through which the antipsychotic agents provide benefit in the treatment of schizophrenia, it is thought that their efficacy is mediated through a combination of antagonist activity at dopamine type 2 and serotonin type 2 receptors.

Most of the warnings and precautions associated with using asenapine and iloperidone 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. Other shared warnings and precautions include the potential for cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis.

The effectiveness and safety of asenapine and iloperidone in patients younger than 18 years of age have not been established.

Asenapine and iloperidone are considered on an individual basis below.

**Asenapine** (Saphris—Schering) is classified as a dibenzo-oxepinopyrrole and has properties that are most similar to those of quetiapine, olanzapine, and clozapine. It is administered sublingually and is indicated for use in adult patients for the acute treatment of schizophrenia and the acute treatment of manic or mixed episodes associated with bipolar I disorder. Because a need often exists for using an antipsychotic agent for an extended period of time, the long-term benefits and risks of the drug in individual patients should be periodically reevaluated.

The effectiveness of asenapine in treating schizophrenia was evaluated in three 6-week studies in which placebo and active controls (haloperidol, olanzapine, and risperidone) were
used. In two of the three studies, asenapine demonstrated superior efficacy to placebo. However, in the third study, asenapine could not be distinguished from placebo, whereas a statistically significant difference was observed with olanzapine, the active control. However, the study was not designed to directly compare the new drug with an active control. In a 52-week study, the effectiveness of asenapine was generally similar to that for olanzapine.

The effectiveness of asenapine in treating bipolar disorder was evaluated in two 3-week studies in which placebo and an active control (olanzapine) were used. In one study, both asenapine and olanzapine exhibited significantly greater response and remission rates compared with placebo. In the other study, the response and remission rates with asenapine were higher than those with placebo but were not considered to be substantially different, whereas the response and remission rates with olanzapine were superior to those with placebo.

The adverse events most frequently experienced with asenapine in the studies in patients with schizophrenia include somnolence (13%), akathisia (6%), and oral hypothesia (5%). In the studies in patients with bipolar disorder, the adverse events most often reported included somnolence (24%), dizziness (11%), extrapyramidal symptoms (excluding akathisia; 7%), and increased weight (5%). Approximately 10% of patients treated with the new drug discontinued treatment as a result of an adverse event, a rate that is similar to that with placebo in patients with schizophrenia and higher than the rate for placebo (6%) in patients with bipolar disorder. In the studies in which olanzapine was used as an active control, asenapine was less likely to cause dry mouth and weight gain but more likely to cause dizziness, nausea, akathisia, and oral hypothesia.

The warnings and precautions identified earlier for the use of the atypical antipsychotic agents should be observed for asenapine. In the 52-week study with the new drug, 15% of patients experienced at least a 7% increase in body weight. Adverse events related to glucose metabolism were reported in less than 1% of the participants in both the asenapine and placebo treatment groups, but patients treated with any of the atypical antipsychotic agents should be monitored for symp-toms of hyperglycemia (e.g., polydipsia, polyuria, weakness). Asenapine exhibits an alpha-1 adrenergic receptor antagonist action that may result in orthostatic hypotension and syncope in some patients, and patients should be advised to slowly rise from a seated or recumbent position.

The effects of asenapine on the QT interval were evaluated with the use of doses up to twice the recommended dosage. The drug was associated with increases in the QTc interval ranging from 2 to 5 ms compared with placebo, but no patients experienced a QTc as high as 500 ms. The use of asenapine should be avoided in patients treated with other medications that are known to prolong the QT interval or who have other risk factors for QT prolongation.

If administered in a conventional tablet formulation that is swallowed, the bioavailability of asenapine is very low (<2%). However, when administered sublingually, the bioavailability of a 5-mg dose is 35%. The consumption of water or food in close proximity to the time of drug administration reduces asenapine exposure, and eating or drinking should be avoided for 10 minutes after administration.

Asenapine undergoes extensive biotransformation via direct glucuronidation by UDP glucuronosyltransferase 1A4 and oxidative metabolism (predominately the CYP1A2 pathway). To a lesser extent, it is also a substrate for the CYP3A4 and -2D6 metabolic pathways. Approximately 50% of a dose of the drug is recovered in the urine and 40% in the feces. Dosage adjustment is not necessary in patients with impaired renal function or mild or moderate hepatic impairment. However, in patients with severe hepatic impairment, asenapine exposure is on average seven times higher than it is in patients with normal hepatic function, and the drug is not recommended for use in patients with severe hepatic impairment.

Caution should be observed when asenapine is administered concurrently with fluoxetine, a CYP1A2 inhibitor. The concurrent use of other medications with which asenapine may interact via pharmacokinetic mechanisms is not likely to necessitate an adjustment in dosage of the new drug. The concurrent use of asenapine with paroxetine (e.g., Paxil), a CYP2D6 substrate and inhibitor, has resulted in an almost twofold increase in paroxetine exposure, and treatment should be closely monitored. Because asenapine may cause adverse events such as sedation and dizziness, it must be used with caution in patients who are also taking other central nervous system (CNS)-active drugs. Patients should be advised to avoid alcoholic beverages while being treated with asenapine. In patients being treated with antihypertensive medications, the alpha-1 adrenergic antagonist action of asenapine may result in an excessive reduction of blood pressure.

Asenapine sublingual tablets are supplied in 5- and 10-mg potencies. Patients should be instructed to place the tablet under the tongue and allow it to dissolve completely in the saliva, which occurs within seconds. The tablets should not be crushed, chewed, or swallowed, and patients should not eat or drink for 10 minutes following administration.

In the treatment of patients with schizophrenia, the recommended initial and maintenance dosage is 5 mg twice a day. In the clinical studies, the use of a higher dosage did not result in added benefit but did increase the frequency of certain adverse events. In the treatment of patients with bipolar disorder, the recommended initial and maintenance dosage is 10 mg twice a day. The dosage may be reduced to 5 mg twice a day if adverse events are experienced.

Although the labeled indications for asenapine are the acute treatment of schizophrenia and bipolar disorder, it is generally recommended that treatment be continued beyond the acute response in patients who have responded well to the medication.

**Iloperidone**

Iloperidone (Fanapt—Novartis) is a benzisoxazole derivative and has properties that are most similar to those of risperidone, paliperidone, and ziprasidone. It has been approved for use in the acute treatment of schizophrenia in adult patients.
However, its indication is qualified with the notation that, in choosing among treatments, prescribers should consider the ability of iloperidone to prolong the QT interval and the use of other drugs first. The relegation of the new agent to second-line use is further confirmed by the observation that “prescribers should also consider the need to titrate iloperidone slowly to avoid orthostatic hypotension, which may lead to delayed effectiveness compared to some other drugs that do not require similar titration” (source: iloperidone package insert).

The effectiveness of iloperidone was evaluated in two short-term studies (4 and 6 weeks) in which placebo and active controls (risperidone and ziprasidone) were used. In the 6-week study, patients received iloperidone, risperidone, or placebo. Although iloperidone was determined to be superior to placebo, it was less effective than risperidone, at least during the first 2 weeks of the study. It has been suggested that this difference in efficacy is attributable to the slow titration of dosage that is recommended with the use of iloperidone, compared with the more rapid titration that is possible with risperidone. After the target maintenance dosage is attained, it is likely that the efficacy of iloperidone and risperidone is similar. However, because the only labeled indication for the new drug is the acute treatment of schizophrenia, the delay in attaining its full clinical benefit represents an important disadvantage.

In a 4-week study in which patients received iloperidone, ziprasidone, or placebo, iloperidone was superior to placebo and generally similar in efficacy to ziprasidone, which also needed a slow titration to the target dosage.

The adverse events most frequently experienced with iloperidone in a dosage of 20 to 24 mg/day in the clinical studies included dizziness (20%), somnolence (15%), tachycardia (12%), dry mouth (10%), weight gain (9%), nasal congestion (8%), fatigue (6%), and orthostatic hypotension (3%). The rate of discontinuation of treatment because of adverse events was 5% in both the iloperidone- and placebo-treated groups. In the study in which ziprasidone was also used, iloperidone was less likely to cause sedation, somnolence, extrapyramidal symptoms, akathisia, agitation, and restlessness but more likely to cause dizziness, orthostatic hypotension, tachycardia, weight gain, and nasal congestion. QT prolongation was similar for the two drugs.

The warnings and precautions identified earlier for the use of the atypical antipsychotic agents should be observed for iloperidone. In a dosage of 12 mg twice a day, iloperidone was associated with QTc prolongation of 9 ms, although no severe cardiac dysrhythmias were observed in the clinical studies. The use of iloperidone should be avoided in patients treated with other medications that are known to prolong the QT interval or who have other risk factors for QT prolongation.

Iloperidone exhibits alpha-1 adrenergic receptor antagonist activity that may result in dizziness, orthostatic hypotension, and syncope. The dosage should be slowly titrated over a period of 7 days to the target maintenance dosage. When the dosage was titrated as recommended in the clinical studies, the incidence of syncope was 0.4%, compared with 0.2% in those receiving placebo. In patients receiving a maintenance dosage of 20 to 24 mg/day, the incidence of orthostatic hypotension was 5%, compared with 1% in those receiving placebo. The frequency of orthostatic hypotension and syncope would be expected to be higher if the dosage was titrated more rapidly. Alpha adrenergic blocking activity has also been associated with the occurrence of priapism, and there were three reports of this problem in the clinical studies.

In patients who were treated with iloperidone in a dosage of 20 to 24 mg/day, 18% experienced at least a 7% increase in body weight, compared with 4% of those receiving placebo. Because some patients treated with atypical antipsychotic agents, including iloperidone, have experienced hyperglycemia, patients should be monitored for symptoms of hyperglycemia (e.g., polydipsia, polyuria, weakness).

Following oral administration, iloperidone is rapidly absorbed and peak plasma concentrations occur within 2 to 4 hours. The drug may be administered without regard to food. Iloperidone is extensively metabolized, primarily via the CYP3A4 and -2D6 pathways. Approximately 7% to 10% of whites and 3% to 8% of blacks have a reduced capacity to metabolize CYP2D6 and are designated as poor metabolizers (PMs), whereas most other patients are extensive metabolizers (EMs). One of the metabolites of iloperidone is pharmacologically active and accounts for 20% and 34% of total plasma exposure in EMs and PMs, respectively. In EMs, approximately 60% of a dose of iloperidone is recovered in the urine and 20% in the feces. Dosage adjustment is not necessary in patients with renal impairment. Because iloperidone has not been studied in patients with mild or moderate hepatic impairment, its use is not recommended in patients with hepatic impairment.

The concurrent use of iloperidone with a strong CYP3A4 inhibitor (e.g., clarithromycin, ketoconazole) or CYP2D6 inhibitor (e.g., fluoxetine, paroxetine) will increase the concentration and activity of the new drug, and the dosage of the new drug should be reduced by one-half when it is used in patients being treated with one of these agents. The use of iloperidone with both ketoconazole and paroxetine did not add to the effect of either inhibitor given alone, and the recommendation to reduce the dosage of iloperidone by one-half also applies to this situation.

Because iloperidone may cause adverse events such as dizziness and somnolence, it must be used with caution in patients who are also taking other CNS-active drugs. Patients should be advised to avoid alcoholic beverages while being treated with iloperidone. In patients being treated with antihypertensive medications, the alpha-1 adrenergic antagonist action of iloperidone may result in an excessive reduction in blood pressure.

To reduce the risk of orthostatic hypotension, the dosage of iloperidone must be titrated slowly from a low starting dosage to the target dose range of 6 to 12 mg twice a day. The recommended initial dosage is 1 mg twice a day with daily adjustments made to 2, 4, 6, 8, 10, and 12 mg twice daily on days 2, 3, 4, 5, 6, and 7, respectively. The effectiveness of the drug has been demonstrated in the dosage range of 6 to 12 mg twice a day. The maximum recommended dosage is 12 mg twice a day.
Because of the need for slow dosage titration, the control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared with the action of some other antipsychotic medications that do not require similar dosage titration.

Iloperidone tablets are supplied in 1-, 2-, 4-, 6-, 8-, 10-, and 12-mg potencies.

### Antidiabetic agent

Incretins are naturally occurring hormones that increase insulin secretion 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. However, exenatide is not effective following oral administration and is administered subcutaneously. In late 2006, sitagliptin (Januvia) was marketed as the first of a new class of antidiabetic agents that can be administered orally to increase the action 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.

**Saxagliptin hydrochloride** (Onglyza—Bristol-Myers Squibb; AstraZeneca) is the second DPP-4 inhibitor to be marketed in the United States, and its properties and use are very similar to those of sitagliptin. The specific indication for the new drug is for use as monotherapy or in combination regimens 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 diabetic ketoacidosis.

In the clinical studies, compared with placebo, treatment with saxagliptin provided clinically relevant improvements in glycosylated hemoglobin (A1C), fasting plasma glucose, and 2-hour postprandial glucose. When used as monotherapy, saxagliptin reduced A1C by approximately 0.6% compared with placebo and, when used with metformin, a thiazolidinedione (pioglitazone [Actos], rosiglitazone [Avandia]), or the sulfonylurea gluburide, it reduced A1C by approximately this same percentage compared with placebo plus the other drug. Use of saxagliptin has not been studied in combination with insulin.

The new drug has not been directly compared with sitagliptin in clinical studies, but the reduction of A1C attained with the recommended dosages of the two agents is similar.

Like sitagliptin, saxagliptin is well tolerated, with an overall incidence of adverse events reported in the clinical studies similar to that of placebo. The adverse events reported most often include upper respiratory tract infection (8%), urinary tract infection (7%), and headache (7%). In the study in which saxagliptin was used in combination with a thiazolidinedione, peripheral edema was experienced more frequently (8%) than in the patients receiving placebo instead of the new drug (4%). Although weight gain is sometimes associated with the use of certain antidiabetic agents (e.g., sulfonylureas, thiazolidinediones), substantial changes in weight have not been observed with saxagliptin or sitagliptin.

Hypersensitivity reactions (e.g., urticaria, facial edema) were reported in 1.5% of the patients treated with saxagliptin, although none of these events was considered life threatening or required hospitalization. In the postmarketing experience with sitagliptin, serious hypersensitivity reactions, including anaphylaxis and Stevens-Johnson syndrome, have been reported infrequently, and a warning regarding this risk is now included in the labeling for this agent but not in the labeling for saxagliptin.

The labeling for saxagliptin was revised in late September to include a warning about acute pancreatitis, which has been reported in the postmarketing experience. A warning about this possibility had been added previously to the labeling for exenatide, and saxagliptin should also 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 or a thiazolidinedione. However, their concurrent use with an agent known to cause hypoglycemia (e.g., sulfonylureas) should be closely monitored, and a lower dosage of the latter agent may be required.

The incidence of fractures in patients treated with saxagliptin is slightly higher than in patients receiving placebo (1.0 and 0.6 per 100 patient-years, respectively). However, causality has not been established, and other studies have not demonstrated adverse actions of saxagliptin on bone.

Use of saxagliptin has been associated with a dose-related mean decrease in absolute lymphocyte counts. However, the clinical importance of this response or the implications for patients with lymphocyte abnormalities (e.g., human immunodeficiency virus infection) is not known.

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

Saxagliptin may be administered without regard to food. It is primarily metabolized via the CYP3A4/5 pathways to an active metabolite, 5-hydroxy saxagliptin, that is also a DPP-4 inhibitor with approximately one-half the potency of the parent compound. Approximately 75% of a dose of the drug is excreted in the urine, and the dosage should be reduced in patients with moderate or severe renal impairment. Dosage adjustment is not necessary in patients with hepatic impairment.

The concurrent use of CYP3A4/5 inhibitors and inducers will alter the pharmacokinetics of saxagliptin and its active metabolite. An adjustment in dosage of saxagliptin is not considered necessary when it is used concurrently with a CYP3A4/5 inducer (e.g., rifampin [e.g., Rifadin]) or a moderate inhibitor of CYP3A4/5 (e.g., diltiazem [e.g., Cardizem]). However, strong inhibitors of CYP3A4/5 increase saxagliptin exposure considerably, and the dosage of the new drug should be reduced when it is used concurrently with one of these agents (e.g., ketoconazole [e.g., Nizoral], itraconazole [e.g., Sporanox], clarithromycin [e.g., Biaxin], telithromycin [Kevox], atazanavir [Reyataz], indinavir [Crixivan], nelfinavir [Viracept], ritonavir [Norvir], saquinavir [Invirase]).

The usual dosage of saxagliptin is 5 mg once a day. In...
patients also being treated with a strong CYP3A4/5 inhibitor and in patients with moderate or severe renal impairment or end-stage renal disease requiring hemodialysis, the recommended dosage is 2.5 mg once a day. Saxagliptin is removed by hemodialysis and should be administered following hemodialysis. Renal function should be assessed before initiating treatment and periodically thereafter.

Saxagliptin hydrochloride is supplied in film-coated tablets in quantities equivalent to 2.5 and 5 mg saxagliptin.

**Agent for psoriasis**

Psoriasis is an autoimmune disease characterized by inflammatory skin lesions/plaques that are often painful and can be debilitating. Although milder forms of psoriasis can often be effectively treated with topical corticosteroids and other topically applied agents, moderate to severe forms of the disease often require systemic therapy or phototherapy. Advances in the treatment of psoriasis have included the use of medications that have immunosuppressive activity such as methotrexate; cyclosporine; alefacept (Amevive), which interferes with T-cell activation; and the tumor necrosis factor (TNF) inhibitors etanercept (Enbrel), adalimumab (Humira), and infliximab (Remicade).

Interleukin (IL)-12 and -23 are naturally occurring proteins that are involved in the psoriatic inflammatory process by activating natural killer cells and T-cells. Ustekinumab (Stelara—Centocor Ortho Biotech) is a human monoclonal antibody that is the first medication to selectively bind to these cytokines. It binds with high affinity to the p40 protein subunit of IL-12 and -23, thereby preventing them from binding with their respective receptors and resulting in a decreased inflammatory response. The new drug is indicated for the treatment of adult patients with moderate or severe plaque psoriasis who are candidates for phototherapy or systemic therapy.

The efficacy of ustekinumab was demonstrated in two placebo-controlled studies in which approximately 70% of the patients treated with the drug experienced at least a 75% reduction in the Psoriasis Area and Severity Index (PASI) score (PASI 75) after two doses compared with less than 5% of those receiving placebo. In one of these studies, patients were evaluated for a longer period and approximately 90% of the patients having an initial reduction in PASI score of at least 75% maintained this response through 1 year of treatment.

In a study in which ustekinumab was compared with etanercept, 68% and 74% of patients treated with 45 and 90 mg ustekinumab dosages, respectively, experienced at least a 75% reduction in PASI score compared with 57% of the patients treated with etanercept. Of the patients who did not have a response to etanercept, almost 50% had at least a 75% reduction in PASI score within 12 weeks following subsequent treatment with ustekinumab.

The risks and adverse events associated with the use of ustekinumab are generally similar to those of the TNF inhibitors. Of greatest concern is the potential for serious infection, and treatment with ustekinumab should not be initiated in patients with a clinically important active infection. If a serious infection develops during treatment, treatment with ustekinumab should be suspended until the infection is adequately treated or resolves.

Patients should be evaluated for the presence of a tuberculosis infection before initiating treatment with ustekinumab. The drug should not be used in patients with active tuberculosis, and if latent tuberculosis is identified, antitubercular treatment should be initiated before administering ustekinumab. Individuals who have a genetic deficiency of IL-12 and -23 are at greater risk of disseminated infections caused by mycobacteria, salmonella, and Bacillus Calmette-Guérin (BCG) vaccinations. Whether patients experiencing inhibition of these interleukins as a result of ustekinumab treatment will be more vulnerable to these infections is not known. However, it is recommended that BCG vaccines not be administered during treatment with ustekinumab or for 1 year before initiating treatment or 1 year following discontinuation of treatment. Before initiating treatment with ustekinumab, patients should have already received the immunizations recommended by current guidelines, and they should not receive live vaccines during treatment.

Like other medications that exhibit an immunosuppressive action, ustekinumab may increase the risk of malignancies. The safety of its use in patients who have a known malignancy or a history of malignancy has not been evaluated.

In the clinical studies with ustekinumab, which included more than 3,500 patients, one patient developed reversible posterior leukoencephalopathy syndrome (RPLS). Treatment was discontinued, and the patient fully recovered with appropriate management. If neurologic or other manifestations suggestive of RPLS occur in patients treated with the new drug, therapy should be discontinued.

The adverse events experienced most often in the clinical studies with ustekinumab include nasopharyngitis (7%), headache (5%), upper respiratory tract infection (4%), and fatigue (3%).

As with all biological therapies, a concern exists regarding immunogenicity. Because ustekinumab has such a long half-life and its presence in the blood interferes with the antibody assay, many of the test results were inconclusive. Of the approximately 2,000 patients screened, less than 5% had positive antibody results, indicating a low risk of immunogenicity.

Ustekinumab is classified in Pregnancy Category B and should only be used during pregnancy if the anticipated benefit outweighs the risk to the fetus. It is likely that the new drug is excreted in human milk, and caution should be exercised if it is administered to a woman who is nursing. The effectiveness and safety of ustekinumab in patients younger than 18 years of age have not been evaluated.

Ustekinumab is administered subcutaneously and is intended for administration under the supervision of a physician for patients who will have regular follow-up visits. In contrast, etanercept and most other medications that are
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given subcutaneously are self-administered by patients. Ustekinumab has a long duration of action and injections are administered every 12 weeks during maintenance treatment, whereas etanercept is usually administered once a week and adalimumab every 2 weeks.

The recommended dosage of ustekinumab for patients weighing 100 kg or less is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks. For patients weighing more than 100 kg, the recommended dosage is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks. The use of the new drug has not been evaluated for periods of treatment beyond 2 years.

Ustekinumab is supplied in single-use vials containing 45 mg (in 0.5 mL) and 90 mg (in 1 mL) of the drug. The vials should be refrigerated.

Agent for allergic conjunctivitis

Allergic conjunctivitis is the most common type of ocular allergy and is usually characterized by signs and symptoms such as itching, redness, burning, tearing, and lid edema. The drugs that have been used in ophthalmic formulations in treating allergic conjunctivitis include antihistamines (e.g., emedastine [Emadine]), mast cell stabilizers (e.g., nedocromil [Alocril]), the dual-acting antihistamine/mast cell stabilizers (azelastine [Optivar], epinastine [Elestat], ketotifen [Alaway, Zaditor], olopatadine [Pataday, Patanol]), the nonsteroidal anti-inflammatory drug ketorolac (Acular), and corticosteroids.

Bepotastine besilate (Bepreve—Ista) is an antihistamine and an inhibitor of the release of histamine from mast cells. Its properties and use are most similar to those of azelastine, epinastine, ketotifen, and olopatadine, and it is indicated for ophthalmic use for the treatment of itching associated with signs and symptoms of allergic conjunctivitis.

The effectiveness of bepotastine was demonstrated in two studies in which it was more effective than its vehicle for reduction of symptoms beyond 2 years.

Ustekinumab has a long duration of action and injections are administered every 12 weeks during maintenance treatment, whereas etanercept is usually administered once a week and adalimumab every 2 weeks.

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To obtain 2.0 contact hours of continuing pharmacy education credit (0.2 CEU) for “New therapeutic agents marketed in the second half of 2009: Part 1,” go to www.pharmacist.com and take your test online for instant credit. CPE processing is free for APPhA members and $15 for nonmembers. A Statement of Credit will be awarded for a passing grade of 70% or better. You have two opportunities to successfully complete the posttest. Pharmacists who complete this exercise successfully before March 1, 2013, can receive credit.

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Assessment Questions

Instructions: The assessment test for this activity must be taken online; please see "CPE processing" below for further instructions. There is only one correct answer to each question. This CPE will be available at www.pharmacist.com no later than March 31, 2010.

1. Which of the following drugs is administered sublingually?
   a. Dronedarone
   b. Bepotastine
   c. Asenapine
   d. Prasugrel

2. Which of the following drugs is administered once a day?
   a. Dronedarone
   b. Bepotastine
   c. Asenapine
   d. Prasugrel

3. Which of the following drugs should be administered with food?
   a. Dronedarone
   b. Saxagliptin
   c. Iloperidone
   d. Prasugrel

4. Which of the following drugs is most likely to be associated with the occurrence of orthostatic hypotension when treatment is initiated?
   a. Ustekinumab
   b. Iloperidone
   c. Saxagliptin
   d. Prasugrel

5. Which of the following drugs is most likely to be associated with a mild taste following administration?
   a. Ustekinumab
   b. Saxagliptin
   c. Prasugrel
   d. Bepotastine

6. With the use of which of the following agents is a loading dose used to initiate treatment?
   a. Iloperidone
   b. Saxagliptin
   c. Prasugrel
   d. Dronedarone

7. Which of the following drugs acts by inhibiting interleukin-12 and -23?
   a. Saxagliptin
   b. Ustekinumab
   c. Asenapine
   d. Bepotastine

8. Which of the following statements is correct regarding prasugrel?
   a. It is extensively metabolized via the cytochrome P450 (CYP)2C19 pathway.
   b. It is a prodrug that is converted to ticlopidine following administration.
   c. It is more effective than clopidogrel in reducing the occurrence of fatal myocardial infarctions.
   d. Its use is contraindicated in patients with a history of transient ischemic attacks or stroke.

9. Which of the following statements is correct regarding prasugrel?
   a. Concurrent use with omeprazole is contraindicated.
   b. It should be used in a regimen that also includes aspirin.
   c. It is less likely than clopidogrel to cause bleeding reactions.
   d. Its use should be avoided in patients with impaired renal function.

10. Which of the following statements is correct regarding dronedarone?
    a. It is designated as a Class II antiarrhythmic agent.
    b. It is indicated for the treatment of patients with ventricular flutter or ventricular fibrillation.
    c. It reduces the risk of cardiovascular hospitalization and cardiovascular mortality.
    d. Its use is contraindicated in patients with Class IV heart failure.

11. Which of the following statements is correct regarding dronedarone?
    a. It is classified in Pregnancy Category X and is contraindicated during pregnancy.
    b. It is more likely than amiodarone to cause pulmonary and thyroid adverse events.
    c. It may cause shortening of the QT interval of the electrocardiogram.
    d. It is extensively metabolized via the CYP2D6 pathway.

12. Which of the following statements is correct regarding asenapine?
    a. It is indicated for the acute treatment of schizophrenia and the acute treatment of manic or mixed episodes associated with bipolar I disorder.
    b. It has been demonstrated in comparative studies to be more effective than olanzapine.
    c. Increased weight is the most frequent adverse event associated with its use.
    d. It is excreted unchanged in the urine.
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13. Which of the following statements is correct regarding asenapine?
   a. Treatment should be initiated with a low dosage that is gradually increased over a period of 3 days.
   b. Its action is increased by the concurrent use of probenecid.
   c. Patients should not eat or drink for 10 minutes following its administration.
   d. Its dosage should be reduced in patients with moderate or severe renal impairment.

14. Which of the following statements is correct regarding iloperidone?
   a. It is classified as a serotonin and norepinephrine reuptake inhibitor.
   b. It is indicated for the acute treatment of major depressive disorder and for the acute treatment of bipolar disorder.
   c. It has been demonstrated in comparative studies to be more effective than risperidone.
   d. Its use should be avoided in patients treated with other medications that are known to prolong the QT interval.

15. Which of the following statements is correct regarding iloperidone?
   a. It has been used concurrently with ziprasidone in patients who experience symptoms of both depression and schizophrenia.
   b. It is supplied in a controlled-release tablet formulation that is administered once a day.
   c. Its dosage should be gradually increased over a period of 7 days when treatment is initiated.
   d. Its use is not recommended in patients with renal impairment.

16. Which of the following statements is correct regarding saxagliptin?
   a. It acts as an incretin receptor antagonist.
   b. Its use should be reserved for patients with diabetes for whom metformin has not provided an adequate response.
   c. It is more effective than metformin but is associated with a greater risk of adverse events.
   d. Its use has not been associated with substantial changes in weight.

17. Which of the following statements is correct regarding saxagliptin?
   a. It should be administered at least 1 hour before or 2 hours after a meal.
   b. It is classified in Pregnancy Category D and its use should be avoided in women who are pregnant.
   c. Its dosage should be reduced in patients with moderate or severe renal impairment.
   d. Its action is reduced by the concurrent use of clarithromycin.

18. Which of the following statements is correct regarding ustekinumab?
   a. It is classified as a tumor necrosis factor inhibitor.
   b. It is indicated for the treatment of moderate to severe plaque psoriasis in patients who are candidates for phototherapy or systemic therapy.
   c. It has been demonstrated to be less effective than etanercept in comparative studies.
   d. It should not be used in patients with severe renal impairment.

19. Which of the following statements is correct regarding ustekinumab?
   a. It is administered intravenously.
   b. It is administered every 12 weeks during maintenance treatment.
   c. Its recommended dosage is 90 mg in adults and 45 mg in children younger than 12 years of age.
   d. It is supplied in a syringe unit designed to facilitate self-administration by patients.

20. Which of the following statements is correct regarding bepotastine?
   a. It is indicated for the treatment of itching in patients with allergic conjunctivitis.
   b. It acts as an antibacterial agent and antihistamine.
   c. It is supplied in ophthalmic solution and ointment formulations.
   d. It is supplied in single-use units that do not contain a preservative.

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