Upon completion of this continuing education activity, the pharmacist should be able to achieve these objectives:

1. Recognize new drugs, their dosage forms and routes of administration.
2. Describe the mechanism of action of drugs appropriate to the disease state they are treating.
3. Identify important and relevant potential drug interactions that may occur with the drugs discussed.
4. Identify and discuss any precautions or contraindications that should be considered when evaluating drug use.
5. Counsel patients on the common side effects that may be experienced with drug therapy.

**INTRODUCTION**

For pharmacists, an important aspect of the profession is keeping informed about new drugs as they are developed and introduced to the market. Moreover, the community pharmacist is often the first-contact, health care professional for both general health and drug-related questions. Many physicians may not find time to read new drug information and may know only what they hear directly from the manufacturer or their representatives. Therefore, it is vital that the community pharmacist be cognizant of the newest drug therapies to provide optimal care and education to their patients and prescribers. In 2009, 35 new drugs were approved for use by the Food and Drug Administration. This article will describe the general pharmacology and clinical uses of these new drugs.

Drugs intended for outpatient dispensing are the focus of community pharmacist monitoring and counseling. The 16 new drugs that are administered either orally or topically, and therefore are more likely to be encountered in the pharmacy setting, are presented in Table 1. This table provides trade name, route of administration, strengths, and dosage form. Each year, more drugs self-administered by the parenteral route, usually subcutaneously, become available for patients. Therefore, the community pharmacist must be knowledgeable about these drugs, as well. Table 2 provides similar information for the 13 newly approved parenteral drugs. Many community pharmacists now provide immunizations to their patients. Six new vaccines were approved for use during 2009. These are summarized.
in Table 3. This article will focus on the drugs most likely to be encountered in a community pharmacy setting. When patients seek counseling on clinic or in patient medications, the pharmacist should consult appropriate references to further educate patients.

The orally and topically administered drugs will be discussed as follows, with the focus on their mechanism of action, basis for therapy, common side effects, general counseling information, and any warnings, precautions, or monitoring that should be routine for the individual drugs.

### Ophthalmic Agents

**Bepotastine** (Bepreve) is used to provide relief from the ophthalmic signs and symptoms of allergic conjunctivitis. It is classified as a second generation antihistamine with typical H1 blocking activity and minimal ability to cross the blood brain barrier. Additional actions that may contribute to its effectiveness include mast cell stabilization and inhibition of leukotrienes, both of which would also decrease local allergic reactions. Side effects associated with bepotastine include an ability to taste the drug shortly after administration, with up to half the patients using the drug reporting this effect. Other side effects, such as eye irritation and headache, occur much less frequently. As a locally administered drug, there is minimal risk of additional side effects or drug interactions. Patients should remove contact lenses prior to administration and wait 10 minutes before reinserting contact lenses. Bepotastine does not treat contact lens induced eye irritation. Bepotastine is available by prescription only and administered at a dose of one drop into affected eye(s) twice daily.

**Besifloxacin** (Besivance) is an ophthalmic suspension antibiotic indicated for the treatment of bacterial conjunctivitis. Administered three times daily, at least four hours apart, for seven days, it is used for the treatment of local ophthalmic infections caused by susceptible organisms. Other ophthalmic fluoroquinolones are administered more frequently, typically four times daily. Besifloxacin is a fluoroquinolone antibiotic and, like other drugs in the class, exerts its effect by inhibiting bacterial DNA gyrase, thus preventing bacterial DNA replication. It is considered a broad spectrum antibiotic and is bactericidal in its activity. Side effects are minimal, with less than 2 percent of patients reporting headache, redness or irritation of the eye, or blurred vision as adverse drug reactions. Patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Dosage Form</th>
<th>Strength(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bepotastine besilate</td>
<td>Bepreve</td>
<td>ISTA Pharmaceuticals</td>
<td>Ophthalmic solution</td>
<td>1.5%</td>
</tr>
<tr>
<td>Besifloxacin hydrochloride</td>
<td>Besivance</td>
<td>Bausch &amp; Lomb</td>
<td>Ophthalmic suspension</td>
<td>0.6%</td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>Ulesfia</td>
<td>Sciele Pharma</td>
<td>Topical lotion</td>
<td>5%</td>
</tr>
<tr>
<td>Artemether/</td>
<td>Coartem</td>
<td>Novartis</td>
<td>Oral tablets</td>
<td></td>
</tr>
<tr>
<td>Lomefloxine</td>
<td></td>
<td></td>
<td></td>
<td>Artemether, 20 mg Lumefloxine, 120 mg</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Saphrix</td>
<td>Schering Plough</td>
<td>Sublingual tablets</td>
<td>5 mg</td>
</tr>
<tr>
<td>Dronedarone</td>
<td>Multaq</td>
<td>Sanofi Aventis</td>
<td>Oral tablets</td>
<td>400 mg</td>
</tr>
<tr>
<td>Everolimus</td>
<td>Afinitor</td>
<td>Novartis</td>
<td>Oral tablets</td>
<td>5 mg</td>
</tr>
<tr>
<td>Febuxostat</td>
<td>Uloric</td>
<td>Takeda</td>
<td>Oral tablets</td>
<td>40 mg, 80 mg</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Fanapt</td>
<td>Vanda</td>
<td>Oral tablets</td>
<td>1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Savella</td>
<td>Forest</td>
<td>Oral tablets</td>
<td>12.5 mg, 25 mg, 50 mg, 100 mg</td>
</tr>
<tr>
<td>Pazopanib hydrochloride</td>
<td>Votrient</td>
<td>GlaxoSmithKline</td>
<td>Oral tablets</td>
<td>200 mg, 400 mg</td>
</tr>
<tr>
<td>Pitavastatin calcium</td>
<td>Livalo</td>
<td>Kowa</td>
<td>Oral tablets</td>
<td>1 mg, 2 mg, 4 mg</td>
</tr>
<tr>
<td>Prasugrel hydrochloride</td>
<td>Effient</td>
<td>Lilly</td>
<td>Oral tablets</td>
<td>5 mg, 10 mg</td>
</tr>
<tr>
<td>Saxagliptin hydrochloride</td>
<td>Onglyza</td>
<td>Bristol Myers Squibb</td>
<td>Oral tablets</td>
<td>2.5 mg, 5 mg</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>Samsca</td>
<td>Oksuka</td>
<td>Oral tablets</td>
<td>15 mg, 30 mg</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Sabril</td>
<td>Lundbeck</td>
<td>Powder for oral solution</td>
<td>500 mg</td>
</tr>
</tbody>
</table>

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Table 1. New orally and topically administered drugs approved in 2009
should avoid contact lens use while treating eye infections or during besifloxacin therapy.

**TOPICAL AGENTS**

*Benzyl alcohol* (Ulesfia), formulated as a 5 percent lotion, is indicated for the treatment of head lice infestation in patients age 6 months and older. Benzyl alcohol’s mechanism of action is different from other pesticide-based head lice treatments. The benzyl alcohol component acts as a paralytic agent on the respiratory spiracles of the louse, allowing the drug’s vehicle to block or “clog” this respiratory apparatus, asphyxiating the louse. One potentially beneficial consequence of this different mechanism is that resistance may be less likely to develop compared with the currently available anti-lice preparations, and it is less likely to cause allergic reactions. Benzyl alcohol should be applied to dry hair to saturate the scalp and hair and then rinsed out after 10 minutes. Note, however, that a larger volume of benzyl alcohol must be used compared with other lice treatments. The product is supplied in eight-ounce bottles. Patients with short hair should use four to eight ounces, while those with extremely long hair may require up to 48 ounces (six bottles). Repeated the application in one week to treat any lice that may have hatched following the initial therapy. Wash all clothing, sheets, towels, combs, and any other item that may come in contact with lice in hot water. Side effects include eye irritation (the patient and the caregiver, if applicable, should avoid ophthalmic exposure to the medication), skin irritation, pruritis and, in some patients, a local anesthetic or hypoesthetic effect.

**Table 2. New parenteral drugs approved in 2009**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Availability</th>
<th>Route*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abobotulinumtoxin A</td>
<td>Dysport</td>
<td>Tercica</td>
<td>300 unit, 500 unit single use vials</td>
<td>IM</td>
</tr>
<tr>
<td>Antithrombin</td>
<td>Atryn</td>
<td>Ovation</td>
<td>1750 unit single dose vials</td>
<td>IV</td>
</tr>
<tr>
<td>C1 esterase inhibitor</td>
<td>Berinert</td>
<td>CSL Behring</td>
<td>500 unit single dose vials</td>
<td>IV</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>Ilaris</td>
<td>Novartis</td>
<td>180 mg single use vials</td>
<td>SC</td>
</tr>
<tr>
<td>Ecallantide</td>
<td>Kalbitor</td>
<td>Dyax</td>
<td>10 mg/ml, 3 ml single use vials</td>
<td>SC</td>
</tr>
<tr>
<td>Fibrinogen concentrate</td>
<td>RiaSTAP</td>
<td>CSL Behring</td>
<td>1 G (900–1300 mg) single use vials</td>
<td>IV</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Simponi</td>
<td>Ortho Biotech</td>
<td>50 mg/0.5 ml single dose syringes</td>
<td>IV</td>
</tr>
<tr>
<td>Interferon beta 1B</td>
<td>Extavia</td>
<td>Novartis</td>
<td>0.3 mg/3 ml single use vials</td>
<td>IV</td>
</tr>
<tr>
<td>Ofatumumab</td>
<td>Arzerra</td>
<td>GlaxoSmithKline</td>
<td>20 mg/ml, 10 ml single use vials</td>
<td>IV</td>
</tr>
<tr>
<td>Pralatrexate</td>
<td>Folotyn</td>
<td>Allos Therapeutics</td>
<td>20 mg/ml, 1 ml and 2 ml single use vials</td>
<td>SC</td>
</tr>
</tbody>
</table>

*Routes: IM = intramuscular, IV = intravenous, SC = subcutaneous

**Table 3. New vaccines approved in 2009**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1N1 (Influenza A)</td>
<td>Agriflu</td>
<td>Novartis</td>
<td>Prevention of the H1N1 (swine) flu</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Fluzone HD</td>
<td>Sanofi Pasteur</td>
<td>Prevention of seasonal flu</td>
</tr>
<tr>
<td>Human papillomavirus</td>
<td>Cervarix</td>
<td>GlaxoSmithKline</td>
<td>Prevention of cervical cancer</td>
</tr>
<tr>
<td>Haemophilus B conjugate</td>
<td>Hiberix</td>
<td>GlaxoSmithKline</td>
<td>Pediatric booster for H. flu type B</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Ixiaro</td>
<td>Intercell Biomedical</td>
<td>Prevention of Japanese encephalitis</td>
</tr>
</tbody>
</table>
ANTI-INFEKTIVE AGENTS

Artemether/Lumefantrine (Coartem) is indicated for the treatment of acute uncomplicated malaria in patients who weigh 5 kilograms or more. This combination was developed specifically to counter the high level of drug resistance that was developing to older antimalarials, such as quinine and mefloquine. Unlike these older drugs, this combination is not indicated for the prevention of malaria. Artemether represents a new class of drugs derived from the native Chinese plant Artemesia annua, whose exact mechanism of action is unknown. Lumefantrine is thought to work in a manner similar to the older drugs such as quinine. However, pharmacodynamically both drugs are ultimately working to inhibit nucleic acid function in the malarial protozoa. The course of therapy is six doses of the combination product over three days, with an initial dose followed by a second dose eight hours later and then twice daily (morning and evening dose) for two days. Dosage is weight based and the average adult dose for patients weighing 35 kg and over (greater than 77 pounds) is four tablets per dose for six doses. The combination should be taken with food to enhance the absorption of both drugs. Both drugs are metabolized primarily through the CYP 3A4 pathway. Therefore, the patient should be monitored for enhanced side effects or toxicities when therapy is concurrent with inhibitors of that system, commonly macrolide antibiotics, protease inhibitors, azole antifungals, calcium channel blockers and cimetidine. Common side effects occurring in more than 25 percent of patients include weakness, dizziness, headache, nausea, and joint or muscle pain. Sleep disturbances are also reported at a relatively high rate. Additionally, a lengthening of the QT interval and potentially life threatening torsade de pointes type arrhythmias may occur.

CARDBOVASCULAR AGENTS

Dronedarone (Multaq) is one of the three new cardiovascular drugs to be approved in 2009. Dronedarone is indicated for the treatment of paroxysmal or persistent atrial fibrillation or flutter. There is a black box warning for dronedarone, contraindicating its use in either NYHA Stage IV heart failure or NYHA Stage II/III heart failure patients who are decompensated. Its use in these patients is associated with a drastic increase in mortality. Mechanistically, dronedarone exhibits all four mechanisms (sodium channel blockade, adrenergic antagonism, potassium channel blockade and calcium channel blockade) of the standard Vaughan Williams classification scheme. Its antiarrhythmic actions arise from all four mechanisms, but it is unknown which is the predominant action. Dronedarone is given with meals twice daily. The most common side effects of dronedarone include diarrhea, weakness, nausea, and rash. It is often compared to amiodarone. In light of this comparison, dronedarone lacks the thyroid, hepatic, ocular and pulmonary toxicities of the older drug and incidence of rash and diarrhea is less. There have been no reports of the signature blue-gray skin discoloration associated with amiodarone use. Unlike amiodarone, it can be used in patients who are hypersensitive to iodine. It may cause arrhythmias and exhibit an additive effect on QT prolongation with other antiarrhythmic drugs. Caution should be taken when the patient is taking multiple antiarrhythmic drugs. Additionally, dronedarone’s primary route of metabolism is through the CYP 3A4 pathway, and therefore the potential for drug interactions exists.

Dronedarone is a Pregnancy Category X drug and should never be administered to pregnant patients, or patients who are planning to become pregnant or who may become pregnant, because of a high risk of skeletal defects. Patients who develop signs of worsening heart failure, such as acute weight gain or edema and increasing shortness of breath, should be advised to consult their physician.

Prasugrel (Effient) is an antiplatelet drug similar in action to clopidogrel, acting as an ADP antagonist to inhibit platelet aggregation. Prasugrel is indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome. It is more effective than clopidogrel but exhibits a higher rate of bleeding. This results in a black box warning prohibiting its use in patients with active bleeding (such as peptic ulcer) or who have suffered from a transient ischemic attack or stroke, and strongly discouraging its use in patients more than 75 years old. Additionally, prasugrel should be discontinued at least seven days prior to scheduled surgery to reduce the risk of bleeding. Patients should inform physicians and dentists about prasugrel therapy so they can consult with the prasugrel prescriber before any procedure to determine if prasugrel should be discontinued for the procedure. Clinically, it is
used for more severe cases and is indicated only in acute coronary syndrome. It is a prodrug and is bioactivated via the CYP 3A4 and CYP 2B6 pathways (with lesser bioactivation by the CYP 2C9 and CYP 2C19 pathways). Therefore, inhibitors of these pathways could diminish the effects of prasugrel. Apart from bleeding risk, the side effect profile of prasugrel is not significantly different from placebo. Prasugrel therapy is initiated with a loading dose of 60 mg and is then taken as 10 mg once daily without consideration to meals. Patients without contraindications should also adhere to a daily aspirin regimen of 75–325 mg. Counsel patients on the signs and symptoms of bleeding, as well as on a rare but serious side effect, TTP.

**Pitavastatin** (Livalo) is the newest HMg CoA reductase inhibitor indicated for the treatment of hyperlipidemias. Doses of pitavastatin should not exceed 4 mg once daily because of a dose dependent incidence of rhabdomyolysis. Pitavastatin is similar in its clinical responses to the other newer drugs of this class (atorvastatin, rosuvastatin) in lowering total cholesterol, LDL and triglycerides, and in modestly elevating HDL. Its primary pharmacodynamic effects result from hepatic LDL receptor up regulation that follows the initial decrease in de novo cholesterol synthesis that is mediated by HMG CoA reductase inhibition. Side effects at recommended doses include gastrointestinal effects (including diarrhea or constipation), headache and joint pain. As noted previously, severe myotoxicity may occur at higher doses, as with other drugs in the class. Monitor for liver enzyme abnormalities before and during therapy. Pitavastatin metabolism is not mediated to any great extent through the cytochrome P450 system. Therefore, it is less likely to be the target of drug interactions that could increase this risk. It is classed as a Pregnancy Category X drug because of possible birth defects and/or spontaneous abortion.

**RENNAL AGENTS**

**Tolvaptan** (Samsca), approved for the treatment of hyponatremia, acts as an antagonist at the renal V₂ vasopressin receptor. Patients who are hypervol-
reported side effect is mild headache. Another side effect of saxagliptin is hypoglycemia. The dose may need to be decreased when given in conjunction with sulfonylureas because of increased risk of hypoglycemia. Saxagliptin is taken once daily without regard to meals.

**MUSCULOSKELETAL AGENTS**

**Febuxostat** (Uloric) is a new xanthine oxidase inhibitor indicated for the treatment of hyperuricemia in patients with gout. Its mechanism of action is the same as allopurinol, decreasing the synthesis of uric acid and thus lowering plasma urate levels, preventing attacks of gout. It also inhibits the enzyme xanthine dehydrogenase, although the significance of this action to clinical benefit is not known. Although it is metabolized by several cytochrome P<sub>450</sub> systems, febuxostat is not the target of clinically significant drug interactions. However, by virtue of its mechanism, it may cause drug interactions with 5 mercaptopurine, azathioprine, and theophylline, increasing the risk of side effects and toxicities of those drugs by inhibiting their metabolism. Side effects are similar to allopurinol and include mild joint pain, rash and modest increases in liver enzymes. ALT and AST should be monitored at two and four months, then periodically thereafter. It could be effective in patients who are not well controlled with allopurinol. Patients may experience gout flares upon initiation of febuxostat. Counsel patients on flare management. NSAIDs or colchicine may be useful to avoid discontinuation of antihyperuricemic agent. Unlike allopurinol, which must be taken in divided doses, febuxostat can be taken once daily and without regard to meals or antacids.

**ANTIPSYCHOTIC AGENTS**

**Asenapine** (Saphris) is an atypical antipsychotic agent indicated for the treatment of bipolar disorder and schizophrenia in adult patients. There is a black box warning against using this agent in the treatment of dementia related psychosis because of increased risk of suicide in these elderly patients. Asenapine demonstrates antagonist action at numerous adrenergic, dopaminergic, histaminergic and serotonergic receptors. However, as with other antipsychotic drugs, its primary benefit is thought to be from the blockade of dopamine at the D<sub>2</sub> and serotonin at the 5-HT<sub>2A</sub> receptors. The most common side effects reported are extrapyramidal side effects and drowsiness. Asenapine is less likely to cause weight gain and has fewer drug drug interactions than some of the other atypical antipsychotic agents. Asenapine may prolong the QT interval and while this is usually mild when asenapine is administered alone, coadministration with other drugs that also lengthen the QT interval could lead to additive effects and arrhythmias. Additionally, additive CNS depression will occur with any drugs that have this effect. Asenapine is taken twice daily without food. The tablet dissolves completely sublingually, and patients should wait 10 minutes before having any food or drink. Patients receiving asenapine should be reminded that the dosage form is a sublingual tablet, and the medication should not be chewed or swallowed. Patients should open the tablet pack only when ready to take their dose and handle the tablet with dry hands. Patients should take care not to break the tablet by pushing it through the tablet pack. Instruct them to peel back the colored tab and remove the tablet with dry hands.

**Iloperidone** (Fanapt) is another new antipsychotic agent, approved in 2009 only for the treatment of schizophrenia in adults. However, it is very similar to asenapine in its mechanism of action, also affects QT interval, and carries the same black box warning. It does differ from asenapine in that it is extensively metabolized by the CYP 3A4 and CYP 2D6 pathways, requiring a reduction in dose when coadministered with inhibitors of those pathways. Additionally, more side effects are reported with iloperidone, including orthostatic hypotension, dizziness, and dry mouth. The increased risk of orthostatic hypotension and syncope requires a slow titration. However, there is less risk of extrapyramidal symptoms with this agent. Iloperidone is taken twice daily with or without meals.

**NEUROLOGICAL AGENTS**

**Vigabatrin** (Sabril) is indicated for the treatment of infantile spasms (also known as West or West’s Syndrome), a rare occurrence of seizures in infants (typically less than 1 year old) and in the treatment of refractory partial complex seizures. Vigabatrin is available as a powder for reconstitution, which requires extensive patient counseling on proper use and administration. The pharmacist should consult the product literature and ensure complete understanding of the procedure prior to dispens-
ing the medication. Vigabatrin works by inhibiting the enzyme GABA transaminase, thus blocking the metabolism of GABA, enhancing its inhibitory effects in the CNS, and thus lowering the incidence of seizures. Side effects associated with vigabatrin include GI upset (vomiting, constipation, and diarrhea), sleep disturbances, infection, and irritability. However, the greatest danger with vigabatrin is potential irreversible visual impairment, ranging from blurry vision to total blindness, in up to 30 percent of patients. This effect is difficult to assess in infants. Therefore, there is a black box warning for vigabatrin and it should only be used when the risk of seizures outweighs the risk of potential blindness. It should be noted that vigabatrin has a limited distribution through the SHARE program (Support, Help, and Resources for Epilepsy); the typical community pharmacist may not dispense this medication but should be aware of its presence in the patient population and be familiar with use and side effect profile. Prescribers are required to be registered to prescribe this agent. Additionally, to avoid this potential effect, the lowest possible effective dose should be used and the potential for blindness stressed to all parties.

Milnacipran (Savella) is a serotonin and norepinephrine reuptake inhibitor indicated for the treatment of fibromyalgia. The role that this action plays in central pain suppression is unclear. Similar to the antidepressants, milnacipran carries a black box warning for the potential to cause suicidal tendencies. The most common side effects associated with milnacipran are nausea and constipation. Other side effects include hot flashes, sleep disturbances, nausea, and increased blood pressure. Mild lengthening of the QT interval and mild increases in liver enzymes may also occur. Concomitant administration of drugs with similar actions should be monitored closely, including the ingestion of alcohol. The concomitant use of MAOIs is contraindicated, as is milnacipran use in patients with closed angle glaucoma. Additionally, potentially fatal serotonin syndrome may occur with milnacipran. Patients should be monitored for this possibility, which may be worsened by other drugs including the “triptan” migraine medica-

tions. Milnacipran is taken twice daily and patients initiate therapy in a seven day dose escalation. Discontinuation of therapy should be gradually decreased if possible to avoid withdrawal symptoms.

**ONCOLOGIC AGENTS**

**Everolimus** (Afinitor) is a new orally active drug indicated for the treatment of advanced renal cell carcinoma that is unresponsive to sunitinib or sorafenib therapy. It binds to and inhibits a tyrosine kinase that regulates cell growth, proliferation and other functions, inhibiting these processes. It is thought to be effective in renal cell cancer treatment by inhibiting cancer cell proliferation and decreasing angiogenesis to cancerous tissue. Everolimus is both a substrate for and inhibitor of the CYP 3A4 (and to a lesser extent CYP 2D6) pathway and therefore may lead to drug interactions. Side effects include GI upset (anorexia, nausea, vomiting, and diarrhea), weakness, rash, headache, and peripheral edema. Also, as the drug action has immunosuppressive effects, patients may be at increased risk of infection and should be educated on signs and symptoms to be aware of. Patients taking everolimus should not receive live vaccines for this reason. Everolimus has demonstrated an ability to cause skeletal birth defects in animals and is classified as Pregnancy Category D. Everolimus is taken as a 10 mg dose once daily, at the same time every day, with or without food. Patients with severe side effects may require a dose reduction to 5 mg daily. Everolimus is available only through a limited distribution system that requires patients to be registered.

**Pazopanib** (Votrient) is another new drug indicated for the treatment of advanced renal cell cancer. It, too, is an inhibitor of tyrosine kinase but is less selective in its actions. Pazopanib inhibits the tyrosine kinase second messenger system that mediates vascular endothelial, platelet derived and fibroblast growth factors, as well as cytokine, interleukin, leucocyte, and glycoprotein tyrosine kinases. Its primary benefit in renal cancer is thought to be its ability to inhibit cancer cell proliferation and angiogenesis of cancer tissues. It is metabolized by the CYP 3A4 system, which may lead to drug interactions. Additionally, it is a weak inhibitor of this system and may precipitate drug interactions itself. It may also lengthen the QT interval, so caution should be taken if other drugs are administered that cause this as well. Side effects include anemias, weakness, fatigue, headache, hair discoloration, hyperglycemia, diarrhea, nausea, vomiting, and anorexia. The most serious adverse drug reaction is severe and potentially fatal hepatotoxicity.

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There is a black box warning for this effect and liver function should be determined first in patients before initiating pazopanib. Continue to monitor liver function routinely every four weeks for at least the first four months of therapy, and periodically thereafter. Counsel patients to report yellowing of the skin or whites of eyes (jaundice), darkness of urine, unusual tiredness, or right upper stomach pain. Counsel patients on signs of bleeding, including unusual bruising, bruises and wounds slow to heal, bleeding gums, or dark/black “coffee ground” stools. Women should not be or become pregnant during pazopanib therapy. Help patients manage GI effects such as diarrhea, nausea, and vomiting, and advise patients to contact their physician if they experience moderate to severe or uncontrollable diarrhea. Pazopanib can be given orally once daily, at least one hour before or two hours after a meal.

MONOCLONAL ANTIBODIES

**Golimumab** (Simponi) is a new monoclonal antibody indicated for the treatment of psoriatic arthritis, rheumatoid arthritis, and active ankylosing spondylitis. For rheumatoid arthritis, golimumab is used in combination with methotrexate. There is a black box warning for golimumab for potential immune system suppression. Serious infections leading to hospitalization or death, including tuberculosis (TB), bacterial sepsis, and invasive fungal and other opportunistic infections have occurred in patients receiving golimumab. Special care should be taken to avoid initiation of therapy during an active infection of any kind and patients should be tested for latent TB, and treated if positive, before initiation. During golimumab therapy all patients should be monitored for infection, including TB, even if the initial latent test is negative, and therapy should be discontinued if serious infection or sepsis occurs. There is also a class warning for TNF blockers for potentially fatal lymphoma or other malignancy in children and adolescents. Golimumab is administered as a 50 mg injection subcutaneously once monthly.

Golimumab is a monoclonal antibody for tumor necrosis factor alpha (TNF alpha), binding to the cytokine and inhibiting its action. TNF alpha is known to be a mediator of the responses present in various inflammatory diseases. Side effects reported with golimumab do not differ significantly from those seen with placebo. However, as with any immunosuppressive agent, golimumab has been shown to cause serious infection. Counsel patients on signs and symptoms of infection, and encourage patients to establish a plan with their prescriber to help them decide when to call the physician regarding an infection. Ask patients if they are allergic to latex before dispensing the prefilled syringe. Ask patients to report new or worsening signs of heart failure, demyelinating disease, autoimmune disease, liver disease, cytopenia, or psoriasis.

Patients who are going to self administer golimumab should be thoroughly counseled on aseptic injection techniques before dispensing the drug. Do not microwave the autoinjector or immerse the autoinjector in hot water to speed warming.

**AGENTS FOR INPATIENT OR HEALTH CARE SETTING ADMINISTRATION**

All other parenteral drugs approved during the past year are intended for administration in either a hospital or a clinical setting where immediate monitoring is available. These drugs include, in addition to golimumab, three other monoclonal antibodies. They are canakinumab, ofatumumab, and ustekinumab. The basic pharmacology and side effects of these and other new parenteral products will be briefly summarized as follows.

**Canakinumab** (Ilaris) is indicated for the treatment of Cryopyrin Associated Periodic Syndromes. These are various and distinct syndromes that include Muckle Wells syndrome and familial cold autoinflammatory syndrome, among others. The commonality of each syndrome is mutation in the gene that codes for the protein cryopyrin. These syndromes result in an autoinflammatory condition that is mediated in part by increased production and release of interleukin 1. Canakinumab is a monoclonal antibody specific for interleukin 1b. It binds to the interleukin, preventing the interleukin receptor interaction and thus decreasing interleukin activity. This action diminishes the syndrome associated with abnormal cryopyrin activity. The primary adverse drug reactions associated with canakinumab include increased risk of infection, headache, vertigo, diarrhea, and nausea. Counsel patients on signs and symptoms of infection and encourage patients to establish a plan with their physician or to help them decide when to call their physician regard-
ing an infection. Ask if the patient was tested for TB. Patients with an active infection or chronic infection, including HIV, hepatitis B or C, and TB, should not start canakinumab therapy; therapy should be discontinued if a serious infection develops. Canakinumab should not be taken with another IL 1 blocking drug or a TNF blocker.

**Ustekinumab** (Stelara) is indicated for the treatment of psoriasis. It is a monoclonal antibody specific for immunoglobulin G1, which interacts with interleukins, contributing to inflammatory and immune reactions. Ustekinumab, by binding to the immunoglobulin and preventing its participation in these interleukin mediated events, decreases the inflammatory aspect of acute exacerbation of psoriasis. Ustekinumab requires relatively infrequent dosing, once every 12 weeks. As with other immunosuppressive agents, there is an increased risk of infection. Apart from an increased risk of infection, ustekinumab has few and mild side effects. Before initiating therapy, patients should be tested for latent TB and treated if positive; therapy should not be started or continued if any clinically important infection exists or develops. Counsel patients on signs and symptoms of infection and encourage patients to establish a plan with their physician to help them decide when to call their prescriber regarding an infection. Patients should tell any healthcare provider that they are receiving ustekinumab before receiving any vaccine; live vaccines are contraindicated.

**Ofatumumab** (Arzerra) is a monoclonal antibody indicated for the treatment of chronic lymphocytic leukemia that is unresponsive to other therapy. Ofatumumab is not a first line therapy. It is specific for the CD20 protein found on lymphocytes, including those of cancerous lymphoeytic leukemia cells. Upon binding to the CD20 protein, the abnormal lymphocyte undergoes lysis and cell death. Ofatumumab may cause infusion reactions, including bronchospasm, edema, changes in blood pressure, and angina or infarction, requiring pretreatment with acetaminophen, an antihista-mine, and a corticosteroid. It may also cause cyto-penias such as thrombocytopenia and neutropenia. This immune-compromised patient is at risk for a JC viral infection, the viral cause of progressive multifocal leukoencephalopathy (PML), a potentially fatal consequence of receiving certain monoclonal antibodies. Patients should be monitored for PML, and ofatumumab must be discontinued should signs appear. As with other monoclonal antibodies, there is an increased risk of infection with ofatumumab.

**Pralatrexate** (Folotyn) is indicated for the treatment of cancer, specifically for peripheral T cell lymphoma (PTCL). Pralatrexate is the first drug to be approved for the treatment of PTCL. Pralatrexate is a folic acid analogue that has a mechanism of action similar to methotrexate’s. It inhibits the enzyme dihydrofolate reductase, thus inhibiting DNA synthesis in cancer cells and limiting cancer cell proliferation. Pralatrexate’s primary and dose limiting toxicity is bone-marrow suppression. It may also cause mucositis, muscle weakness, anemia, GI effects, and fatigue. Counsel patients to watch for signs and symptoms of mucositis, such as swelling and redness in their mouth, extra sensitivity to warm or spicy food, or mouth sores that make eating difficult. Good oral care can help reduce risk or delay onset of mucositis. Refer patients to their dentist or a dentist familiar with cancer oral care. A simple saline rinse after meals and at bedtime (one teaspoon salt in four cups water) will help remove debris and moisten the mouth. Instruct patients to take folic acid and vitamin B12 supplements (some may receive B12 injection) to mitigate possible side effects. Pralatrexate is a Pregnancy Category D drug, known to cause birth defects. It should only be given if the benefits of therapy outweigh the risk of teratogenicity.

**Romidepsin** (Istodax) is another new cancer drug indicated for the treatment of cutaneous T cell lymphoma in patients who have received at least one prior systemic therapy. Romidepsin is known to inhibit the enzyme histone deacetylase, disrupting gene expression. It is unknown how this aids in the treatment of lymphoma. Romidepsin is metabolized primarily via the CYP 3A4 system. For that reason, drug interactions are likely and the dose may have to be decreased in patients receiving CYP 3A4 inhibitors. Adverse drug reactions observed with romidepsin include nausea and vomiting, various anemias, increased risk of infection, and QT prolongation. Romidepsin is a Pregnancy Category D drug, known to cause birth defects. It should only be given if the benefits of therapy outweigh the risk of teratogenicity. Additionally, it binds to estrogen receptors and may reduce the effectiveness of estrogen-containing contraceptives. Counsel women taking estrogen containing contraceptives that they may be more likely to become pregnant (which is
not advised) or experience breakthrough bleeding during romidepsin therapy.

Telavancin (Vibativ) is a new parenteral bactericidal antibiotic indicated for the treatment of complicated skin infections caused by susceptible gram positive organisms, including MRSA. It is a vancomycin derivative and acts in a similar manner, inhibiting bacterial cell wall cross linking. It also binds directly to the bacterial cell wall, further weakening it. Telavancin is potentially nephrotoxic, may prolong QT intervals, and could cause pseudomembranous colitis. Additionally, it may produce a syndrome of intense vasodilatation upon infusion, similar to vancomycin. It may also cause nausea and a metallic or soapy taste. Unlike vancomycin, telavancin can be dosed once daily, does not require serum concentration monitoring, and has a lower risk of ototoxicity. Telavancin has a black box warning against use during pregnancy because of the risk of fetal harm. Physicians or patients themselves may enroll in the VIBATIV pregnancy registry by calling 888-658-4228. Telavancin has demonstrated limb and digit malformation in animal studies, but human studies have excluded pregnant women. Women of child bearing potential (who have functional ovaries, fallopian tubes, and a uterus and have not had complete absence of menses for 24 months) should have a pregnancy test before initiation of therapy. One or more contraceptive methods should be used during telavancin therapy. Patients should be counseled on the potential risk of fetal harm if pregnancy occurs on telavancin therapy, and they should immediately report any suspected or confirmed pregnancy. Counsel patients to immediately report severe diarrhea, especially watery and bloody stool that occurs without stomach cramps and fever—which may occur as late as two months after last dose.

Recombinant antithrombin (ATryn) is for the prevention of thromboembolic events in perioperative and peripartum patients with hereditary antithrombin III deficiency. It is used as a physiological replacement product in these patients. It is not indicated for the treatment of thromboembolic event in hereditary antithrombin deficient patients. Antithrombin is a normal constituent of the hemostasis system whose function is to prevent excessive clot formation by inhibiting thrombin. Replacement in patients deficient in antithrombin will reduce thromboembolus formation often associated with surgery or childbirth. Heparin and the derived low molecular weight heparins require antithrombin for efficacy. Therefore, an additive anticoagulant effect could be seen with their coadministration. Patients should be monitored for possible bleeding events.

Recombinant antithrombin is administered as an intravenous infusion. The primary adverse drug reaction associated with antithrombin is hemorrhage, an extension of its action. Other side effects include dizziness, chest tightness, and nausea. Recombinant antithrombin use is contraindicated in patients with goat milk hypersensitivity.

Conversely, Fibrinogen (factor 1) (RiaStap) concentrate is approved to treat acute bleeding episodes in patients with a fibrinogen deficiency. Therefore, as opposed to recombinant antithrombin, fibrinogen concentrate is used to promote clot formation. Thrombin activates fibrinogen’s conversion to fibrin, and thus promotes clot formation and prevents blood loss. In patients with fibrinogen deficiency who present with excessive bleeding, fibrinogen concentrate is administered as a replacement product. The most common side effects associated with fibrinogen administration are fever and headache. Anaphylactic reactions have also been reported, but the primary adverse drug reaction of concern is excessive activity resulting in thromboembolic events. Counsel patients on the signs and symptoms of thromboembolus (clot) such as chest or leg pain, leg swelling, coughing up blood, shortness of breath or other trouble breathing, and neurologic changes. Any signs and symptoms of thromboembolus should be immediately reported to a physician or an emergency facility, notifying the emergency personnel of a fibrinogen therapy history. Fibrinogen is administered intravenously.

Ecallantide (Kalbitor) and C1 esterase inhibitor (Berinert) are both approved for the treatment of acute angioedema in adolescents and adults. Patients diagnosed with hereditary angioedema form excessive kallikrein, which is thought to contribute to the profound facial and abdominal edema associated with the condition. Kallikrein is a complement pathway component of both the hemostasis and inflammatory cascade systems, and it is a powerful vasodilator that increases vascular permeability. Patients with familial angioedema are often deficient in C1 esterase inhibitor, a component of the immune system that regulates formation of kallikrein. C1 esterase inhibitor is effective in
treating angioedema by preventing the excessive formation of kallikrein. Side effects associated with C1 esterase inhibitor include nausea and vomiting, abdominal pain and taste perversion. Doses of C1 esterase inhibitor that are greater than recommended have resulted in thromboembolic events. Additionally, as C1 esterase inhibitor is derived from human blood donations, there is a slight risk of bloodborne disease. C1 esterase inhibitor may be self-administered by a skilled patient. Counsel patients to have adequate supplies for administration, and assess their preparedness to manage hypersensitivity reactions. Ecallantide is effective by reversibly inhibiting kallikrein. Both drugs inhibit kallikrein mediated vasodilation and subsequent increased vascular permeability. Some patients receiving ecallantide have demonstrated anaphylactic allergic reactions, and ecallantide carries a black box warning about this effect. Other side effects associated with ecallantide are not significantly greater than placebo but may include GI upset, headache, and injection site reactions.

Abobotulinum toxin A was approved in 2009 and specifically indicated for the treatment of cervical dystonia and cosmetic reduction of the appearance of glabellar lines on the forehead. There are also numerous off label uses for botulinum toxin to accomplish both therapeutic and cosmetic outcomes, but these off label uses will not be discussed here. Abobotulinum toxin acts by binding to the synaptic storage vesicles of acetylcholine and preventing its release into the synaptic cleft. This essentially decreases cholinergic neurotransmission at the neuromuscular junction, causing a partial chemical denervation of the postsynaptic muscle. This results in reduced muscle tone. In cervical dystonia, this relieves the patient of abnormal pain associated with overcontraction of the neck muscles. There is a black box warning for botulinum toxin toxicity. Some patients receiving botulinum toxin as a treatment have experienced classic signs of botulism, including an inability to swallow and respiratory paralysis, resulting in death. It is thought that despite the local administration of the toxin, it may be distributed to other areas of the body.

Other adverse drug reactions reported with botulinum toxin include cardiac events (including arrhythmias and infarction) that may be fatal. Drug interaction concerns with botulinum toxin include neuromuscular blockers, aminoglycoside antibiotics and any other drugs that may have neuromuscular blocking activity, since an additive effect could result. The most common side effect is headache. Use is contraindicated in patients with a cow milk allergy. Counsel patients to report trouble speaking, swallowing or breathing; onset of these symptoms may begin anywhere from hours to weeks following injection. Ignoring these symptoms can result in death. Patients with breathing problems, heart disease, diabetes, planned surgery, planned injection-site infection, swallowing problems or a disease of the nervous system should not receive injections. Patients who have had a botulinum toxin product injection previously should tell the provider who will be giving the next injection which product they received and when it was administered.

**CASE STUDY**

John Doe is an active 56-year-old male patient with a history of hypertension and arrhythmia. He also suffers from mild heartburn but has no evidence of gastric or duodenal ulceration and tests negative for *H. pylori*. Until recently, all conditions have been well controlled with his current medications and, specifically, sotalol has been effective in treating both the hypertension and the arrhythmia. He has no history of other chronic disease states, and hepatic and renal functions and blood work are all within normal levels. His current medication profile is as follows:

**Prescription medications**
- Sotalol, 120 mg, bid (for blood pressure and arrhythmias)
- Hydrochlorothiazide, 25 mg qam (for blood pressure)

**Over-the-counter medications**
- Ibuprofen, 400 mg occasionally (for headache or muscle pain)
- Cimetidine, 200–400 mg qd or qod, prn (for heartburn)
- Various antacids, prn (for heartburn)

Recently, however, his arrhythmias have worsened and his physician has noted atrial involvement. The physician has read of the new antiarrhythmic drug dronedarone and
continuing education quiz

Select the correct answer.

1. This drug acts to inhibit bacterial DNA synthesis and replication.
   a. Bepotastine
   b. Telavancin
   c. Besifloxacin
   d. Ofatumumab

2. Dronedarone should not be used in patients with:
   a. Stage IV heart failure
   b. Viral infections
   c. Multiple sclerosis
   d. Hyponatremia

3. Bepotastine is administered by which route?
   a. orally
   b. intramuscularly
   c. Subcutaneously
   d. topically

4. What is an advantage of benzyl alcohol over older lice treatments?
   a. Smaller dose
   b. Less resistance
   c. one treatment is effective
   d. Applied for only three minutes

5. There is a black box warning for tolvaptan for which situation?
   a. PML
   b. Suicide
   c. Hypernatraemia
   d. Torsade de pointes

6. Which of the following is indicated for malaria?
   a. Artemether/Lumefantrine
   b. Besifloxacin
   c. Telavancin
   d. Prasugrel

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7. Relative to clopidogrel, prasugrel differs by which of the following?
   a. It is orally active.
   b. It causes more bleeding.
   c. It is not a prodrug.
   d. It may be given during surgery.

8. This drug is an oral antidiabetic medication.
   a. Asenapine
   b. Vigabatrin
   c. Febuxostat
   d. Saxagliptin

9. Asenapine carries which black box warning?
   a. Suicide
   b. Hepatotoxicity
   c. Blindness
   d. Bleeding

10. Vigabatrin carries a black box warning for which of the following?
    a. Suicide
    b. Hepatotoxicity
    c. Blindness
    d. Bleeding

11. Milnacipran is classified as which of the following?
    a. TCAs
    b. SSRIs
    c. SNRIs
    d. MAOIs

12. Which of the following drugs causes limb/digit malformations as birth defects?
    a. Everolimus
    b. Telavancin
    c. Dronedarone
    d. Saxagliptin

13. The cancer drug pazopanib carries a black box warning for which of the following?
    a. Suicide
    b. Hepatotoxicity
    c. Blindness
    d. Bleeding

14. Golimumab is a monoclonal antibody to which of the following?
    a. CD20 protein
    b. Immunoglobulin G1
    c. Interleukin 1b
    d. Tumor necrosis factor

15. Interferon beta 1b is used to treat which of the following?
    a. Psoriatic arthritis
    b. Cytopyrin periodic syndrome
    c. Renal cell carcinoma
    d. Multiple sclerosis

16. Saxagliptin acts by inhibiting which enzyme?
    a. HMG CoA reductase
    b. Dipeptidyl peptidase
    c. Dihydrofolate reductase
    d. Histone deacetylase

17. Febuxostat works in a manner that is similar to which of the following drugs?
    a. Allopurinol
    b. Vancomycin
    c. Methotrexate
    d. Clopidogrel

For questions 18–19, please consider the following case:

Jane Doe is a 34-year-old female with a history of mild hypertension, hyperlipidemia, and seasonal allergies. Her hypertension is well controlled and her lipids are becoming favorable following a change in medication by her physician. Her current medication profile is as follows:

- Hydrochlorothiazide 25 mg/Triamterine 37.5 mg qd
- Pitavastatin 4 mg, qd
- Desloratidine 5 mg, qd prn

Ms. Doe has recently discovered that she is pregnant. Following a physician’s appointment, she learns that she is seven weeks into her pregnancy.
18. In the case of Ms. Doe, described above, which drug should be immediately discontinued?
   a. Hydrochlorothiazide  
   b. Desloratidine  
   c. Pitavastatin  
   d. Triamterine

19. Which is more likely should her dose of pitavastatin exceed 4 mg?
   a. Bleeding  
   b. Nephrotoxicity  
   c. Viral infection  
   d. Rhabdomyolysis

20. Which of the following is used to treat chronic lymphocytic leukemia?
   a. Ofatimumab  
   b. Everolimus  
   c. Pralatrexate  
   d. Romidepsin

New Drugs of 2009
June 1, 2010 (expires June 1, 2013)
Activity Type: Knowledge-based

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Last 4 digits of SSN    MM-DD of birth

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Quiz: Shade in your choice
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Quiz: Circle your choice
21. Is this program used to meet your mandatory C.E. requirements?  
   a. yes b. no

22. Type of pharmacist:  
   a. owner b. manager c. employee

23. Age group:  
   a. 21–30 b. 31–40 c. 41–50 d. 51–60 e. Over 60

24. Did this article achieve its stated objectives?  
   a. yes b. no

25. How much of this program can you apply in practice?  
   a. all b. some c. very little d. none

How long did it take you to complete both the reading and the quiz? ______ minutes

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