

# New therapeutic agents marketed in the second half of 2009: Part 2

Daniel A. Hussar

## 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. Seven of these agents were reviewed in the first part of this two-part series, and the other seven agents are reviewed in this second part of the series: telavancin, vigabatrin, abobotulinumtoxinA, pazopanib hydrochloride, ofatumumab, pralatrexate, and canakinumab. 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 new drugs are also discussed. When possible, the properties of the new drugs are compared with those of older drugs marketed for the same indications.

**Conclusion:** Some of the new drugs discussed in this article have properties and uses that are very similar to those of older drugs. However, vigabatrin is the first drug to be approved for the treatment of infantile spasms, pralatrexate is the first drug to be approved for the treatment of patients with peripheral T-cell lymphoma, and canakinumab offers several advantages over the one previously marketed drug for the treatment of cryopyrin-associated periodic syndromes. 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.

*Pharmacy Today*. 2010(Apr);16(4):33-43.

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**Disclosure:** The author and APhA's editorial staff declare no conflicts of interest or financial interests in any product or service mentioned in this article, including grants, employment, gifts, stock holdings, or honoraria.

Part 1 of this series appeared in the March 2010 issue of *Pharmacy Today*. The two parts are separate opportunities for obtaining continuing pharmacy education.

## 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**

## Antibiotic

**Telavancin hydrochloride** (Vibativ—Astellas; Theravance) is a lipoglycopeptide antibiotic that is a synthetic derivative of vancomycin (e.g., Vancocin). It acts by inhibiting bacterial cell wall synthesis and also by binding to the bacterial membrane, thereby disrupting membrane barrier function. The new drug exerts a bactericidal action against gram-positive bacteria and has been approved for use via intravenous infusion for the treatment of adult patients with complicated skin and skin structure infections (cSSSIs) caused by susceptible isolates of the following gram-positive bacteria: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), or *Enterococcus faecalis* (vancomycin-susceptible isolates only). Although a possibility exists that telavancin may be active against certain isolates of gram-positive bacteria that are not susceptible to vancomycin or other antibiotics, it appears unlikely to be effective in infections caused by enterococci or staphylococci that are resistant to vancomycin.

The effectiveness of telavancin was evaluated in studies in patients with cSSSIs in which it was compared with vancomycin. The two antibiotics were generally similar in their effectiveness, with telavancin considered to be noninferior to vancomycin. However, the clinical cure rates for telavancin were lower in patients 65 years or older (compared with those <65 years) and in patients with a creatinine clearance of 50 mL/min or less. Reduced cure rates of the same magnitude were not observed in patients receiving vancomycin.

The labeled indications for telavancin are much more limited than those for vancomycin, which is also indicated for infections caused at other sites including endocarditis. The new drug has been determined to be noninferior to vancomycin in studies in patients with hospital-acquired pneumonia caused by gram-positive bacteria. However, this is not a labeled indication at the present time.

Studies of telavancin in several animal species have raised concerns about adverse developmental outcomes. Accordingly, a boxed warning is included in the labeling for telavancin that indicates that women of childbearing potential should have a serum pregnancy test before use of the drug. The new agent is classified in Pregnancy Category C and should be avoided during pregnancy unless the anticipated benefit outweighs the risk to the fetus. In those situations in which there is justification for using telavancin during pregnancy, patients should be enrolled in the pregnancy registry for the drug by calling 888-658-4228.

In the studies in which telavancin was compared with vancomycin, increases in serum creatinine concentrations to 1.5 times baseline occurred more frequently with the new drug (15% vs. 7%). Renal function should be determined before initiation of treatment, during treatment (at 48- to 72-hour intervals or more frequently, if clinically indicated), and at the end of therapy. The dosage should be reduced in patients with impaired renal function, although whether telavancin should

be used at all in these patients should be considered in view of its decreased efficacy in patients with renal impairment. Monitoring serum concentrations of telavancin, as is typically done with the use of vancomycin, is not considered necessary.

Telavancin has been reported to prolong the QT interval of the electrocardiogram, and caution must be observed when it is used in patients being treated with other drugs with a similar potential (e.g., certain antiarrhythmic agents, ziprasidone [Geodon]). The use of the new drug should be avoided in patients with congenital long QT syndrome, known prolongation of the QT interval, uncompensated heart failure, or severe left ventricular hypertrophy.

The adverse events reported most frequently in the clinical studies with telavancin included taste disturbance (33%), nausea (27%), vomiting (14%), and foamy urine (13%). As with vancomycin, the intravenous infusion of telavancin at an excessive rate may result in infusion-related reactions such as "red-man syndrome," characterized by flushing of the upper body, urticaria, pruritus, and/or rash. The effectiveness and safety of telavancin in pediatric patients have not been evaluated.

Although the use of telavancin has not been associated with an increased risk of bleeding, it has been reported to interfere with certain tests used to monitor coagulation, including prothrombin time, international normalized ratio, activated partial thromboplastin time, activated clotting time, and coagulation-based factor Xa tests. It is recommended that blood samples for these coagulation tests be collected as close as possible prior to a patient's next dose of the antibiotic.

Telavancin undergoes only limited metabolism and is primarily eliminated by the kidneys. Approximately 75% of an administered dose is recovered in the urine and less than 1% in the feces. Dosage adjustment is not necessary in patients with mild or moderate hepatic impairment. The drug has not been evaluated in patients with severe hepatic impairment.

Telavancin has a longer duration of action than vancomycin and is administered once every 24 hours. The recommended dosage is 10 mg/kg administered via intravenous infusion during a 60-minute period every 24 hours for 7 to 14 days. In patients whose creatinine clearance is between 30 and 50 mL/min, the recommended dosage is 7.5 mg/kg every 24 hours, and in patients whose creatinine clearance is between 10 and 29 mL/min, the recommended dosage is 10 mg/kg every 48 hours.

Telavancin hydrochloride is supplied in single-use vials containing the equivalent of 250 and 750 mg telavancin base. The vials should be stored in a refrigerator. The lyophilized contents are reconstituted with 15 or 45 mL, respectively, of 5% Dextrose Injection, Sterile Water for Injection, or 0.9% Sodium Chloride Injection, with the resultant solution containing the drug in a concentration of 15 mg/mL. The time for reconstitution is generally under 2 minutes but can sometimes take as long as 20 minutes. The reconstituted solution must be further diluted before infusion. Following reconstitution, the solution should be used within 4 hours when stored at room temperature or within 72 hours when stored in the refrigerator.

Hydroxypropyl-beta-cyclodextrin is used as a solubilizing agent in the formulation of telavancin and may accu-

**Table 1.** New therapeutic agents marketed in the United States from July to December 2009<sup>a</sup>

Generic name	Trade name	Manufacturer	Therapeutic classification	Route of administration	FDA classification <sup>b</sup>
AbobotulinumtoxinA	Dysport	Ipsen	Agent for cervical dystonia	Intramuscular	S <sup>c</sup>
Canakinumab	Ilaris	Novartis	Agent for cryopyrin-associated periodic syndromes	Subcutaneous	P <sup>c</sup>
Ofatumumab	Arzerra	GlaxoSmithKline	Antineoplastic agent	Intravenous	P, O <sup>c</sup>
Pazopanib hydrochloride	Votrient	GlaxoSmithKline	Antineoplastic agent	Oral	1-S
Pralatrexate	Folotyn	Allos	Antineoplastic agent	Intravenous	1-P
Telavancin	Vibativ	Astellas	Antibiotic	Intravenous	1-S
Vigabatrin	Sabril	Lundbeck	Antiepileptic drug	Oral	1-P

<sup>a</sup>Additional agents marketed during this time period are considered in part 1 of this two-part series.  
<sup>b</sup>FDA classification of new drugs: 1 = new molecular entity; O = designated orphan drug; P = priority review; S = standard review.  
<sup>c</sup>A biological approved through an FDA procedure that does not assign a numerical classification.

multate in patients with impaired renal function. However, whether the accumulation of this agent is of clinical importance is not known.

### Antiepileptic drug

Infantile spasms usually appear in the first year of life and primarily consist of a sudden bending forward of the body with stiffening of the arms and legs. Spasms tend to occur upon awakening or after feeding and often occur in clusters of as many as 100 spasms. Infants may experience dozens of clusters and several hundred spasms per day. Agents such as prednisolone and adrenocorticotropic hormone (ACTH) have been used in the treatment of infantile spasms. However, this is not a labeled indication for these agents at the present time, although a supplemental new drug application for this use has been submitted for ACTH.

**Vigabatrin** (Sabril—Lundbeck) is the first drug to be approved for the treatment of infantile spasms and is specifically indicated as monotherapy for pediatric patients (1 month to 2 years of age) with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss. Although the specific mechanism of action of vigabatrin is not known, it is thought to act as an irreversible inhibitor of gamma-aminobutyric acid (GABA) transaminase, the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA. This action results in increased concentrations of GABA in the central nervous system.

The effectiveness of vigabatrin in the treatment of infantile spasms was demonstrated in studies in which infants received either a low or high dosage of the drug. The primary efficacy endpoint was the proportion of patients who were spasm free for 7 consecutive days. Of patients in the high-dose group, 16% achieved spasm freedom compared with 7% of those in the low-dose group. Studies have also demonstrated more than a 50% reduction in seizure frequency in considerably larger percentages of patients. The results of some limited comparative studies suggest that vigabatrin may be less effective than prednisolone or ACTH in some patients.

Vigabatrin has also been approved as adjunctive therapy

for adult patients with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss. Numerous other antiepileptic drugs (e.g., carbamazepine, oxcarbazepine, lamotrigine, levetiracetam) are effective for the treatment of complex partial seizures, and vigabatrin is not indicated as a first-line agent.

The most important risk associated with the use of vigabatrin is permanent vision loss, which may occur in infants, children, and adults and is the subject of a boxed warning in the product labeling. It causes bilateral concentric visual field constriction in 30% or more of patients, ranging in severity from mild to severe. A progressive loss of peripheral vision may be associated with tunnel vision and can result in disability. In some patients, the drug may also damage the central retina and decrease visual acuity. The onset of vision loss is unpredictable and can occur at any time during treatment. Vision should be assessed at baseline and at least every 3 months during therapy. Vision testing is also required approximately 3 to 6 months following discontinuation of therapy.

When used in patients with infantile spasms, the most frequently observed adverse events with vigabatrin included somnolence (45%), bronchitis (30%), ear infection (10%), and acute otitis media (10%). When used in combination regimens in adults with complex partial seizures, the most commonly reported adverse events included headache (18%), somnolence (17%), fatigue (16%), dizziness (15%), convulsion (11%), nasopharyngitis (10%), weight gain (10%), upper respiratory tract infection (10%), visual field defect (9%), nystagmus (7%), blurred vision (6%), diplopia (6%), and depression (8%). As with other antiepileptic drugs, a risk of suicidal ideation and behavior exists, and adult patients should be monitored for the emergence or worsening of depression and/or unusual changes in mood or behavior.

Magnetic resonance imaging abnormalities that involve the thalamus, basal ganglia, brain stem, and cerebellum have been observed in some infants with infantile spasms. However, the relationship to treatment and the potential for long-term clinical sequelae have not been determined. Neurotoxic-

ity has been reported in animal studies and may be characterized by fluid accumulation and separation of the outer layers of myelin (intramyelinic edema). Whether these observations are associated with specific risks when the drug is used in patients is not known.

Vigabatrin is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. It is excreted in human milk, and a decision should be made whether to discontinue nursing or not use the drug.

Vigabatrin increases the activity of the cytochrome P450 (CYP)2C9 metabolic pathway and has been reported to reduce the plasma concentration of phenytoin by approximately 20%. Conversely, the peak serum concentration of clonazepam has been reported to be increased by 30% when vigabatrin is used concurrently. The new drug decreases alanine aminotransferase (ALT) and aspartate aminotransferase (AST) plasma activity in most patients, and this may preclude the use of these markers, especially ALT, in detecting early hepatic injury.

Following oral administration, vigabatrin is almost completely absorbed. It is not substantially metabolized, and approximately 80% of a dose is excreted in the urine in unchanged form.

For use in the treatment of infantile spasms, vigabatrin is supplied as a powder for oral solution in packets containing 500 mg of the drug. The recommended initial dosage is 50 mg/kg/d given in two divided doses. The dosage can be titrated by 25 to 50 mg/kg/d increments every 3 days up to a maximum dosage of 150 mg/kg/d. The entire contents of the appropriate number of packets of powder should be emptied into an empty cup and dissolved in 10 mL cold or room temperature water per packet using the oral syringe supplied with the medication. The concentration of the final solution is 50 mg/mL. Each dose of the medication should be prepared immediately before it is to be administered. Because of the risk of vision loss, vigabatrin should be withdrawn from patients with infantile spasms who fail to show substantial clinical benefit within 2 to 4 weeks of initiation of treatment.

Vigabatrin tablets are supplied in 500-mg potency for use in adult patients with refractory complex partial seizures. The recommended initial dosage is 500 mg twice a day, and the total daily dose may be increased in 500-mg increments at weekly intervals to the target maintenance dosage of 1,500 mg twice a day. In patients with mild, moderate, and severe renal impairment, the dosage should be reduced by 25%, 50%, and 75%, respectively. Information is not available regarding dosage adjustment in pediatric patients with renal impairment.

When treatment with vigabatrin is to be discontinued, the dosage should be gradually reduced. In pediatric patients, the dosage has been reduced at a rate of 25 to 50 mg/kg every 3 to 4 days, and in adults, the daily dose is decreased by 1,000 mg a day on a weekly basis.

Vigabatrin is available only through a restricted distribution program (888-45-SHARE). Only prescribers and pharmacies who are registered in this program may prescribe and dis-

tribute vigabatrin to patients who meet the conditions of and are enrolled in this program.

### Agent for cervical dystonia

Cervical dystonia, also known as spasmodic torticollis, is characterized by involuntary contractions of the muscles of the neck and is often associated with abnormal head position and neck pain. In addition to the pain that afflicts patients, cervical dystonia may have a very negative impact on a patient's quality of life as a result of reduced mobility, diminished self-esteem, embarrassment, social isolation, and/or occupational disability.

Botulinum toxins are neuromuscular blocking toxins, and the marketing of botulinum toxin type B (Myobloc), now designated as rimabotulinumtoxinB, in 2001 represented an important advance in the treatment of cervical dystonia. Shortly thereafter, botulinum toxin A (Botox), now designated as onabotulinumtoxinA, was also approved for the treatment of cervical dystonia. OnabotulinumtoxinA was initially approved by FDA in 1989 for the local treatment of the ocular disorders blepharospasm and strabismus associated with dystonia and was subsequently approved for the treatment of severe primary axillary hyperhidrosis, as well as for cosmetic use.

**AbobotulinumtoxinA** (Dysport—Ipsen) is a purified neurotoxin type A complex produced by fermentation of the bacterium *Clostridium botulinum* type A, Hall strain. Like its two predecessors, when injected into the affected muscles, it inhibits the release of acetylcholine from peripheral cholinergic nerve endings. This interruption of cholinergic transmission results in a localized reduction of muscle activity that gradually reverses over time. The new drug has been approved for the treatment of adult patients with cervical dystonia to reduce the severity of abnormal head position and neck pain in both toxin-naïve and previously treated patients. As with onabotulinumtoxinA, it has also been approved for aesthetic/cosmetic use for the temporary improvement in the appearance of moderate to severe glabellar lines (e.g., "frown lines," "crow's feet") associated with procerus and corrugator muscle activity in adult patients younger than 65 years of age.

The effectiveness of abobotulinumtoxinA in the treatment of cervical dystonia was demonstrated in placebo-controlled studies in which the drug was administered by intramuscular injection divided among two to four affected muscles. The results in the group of patients treated with the medication were statistically significantly greater compared with those receiving placebo. The new drug has not been directly compared with the other botulinum toxin products in clinical studies.

The most important risk of the botulinum toxin products is the potential for distant spread of the toxin effect from the area of injection, and this is the subject of a boxed warning in their labeling. Swallowing and breathing difficulties have been reported hours to weeks after injection and can be life threatening. The risk of these problems is greatest in children treated for spasticity, but symptoms have also occurred in adults, particularly in patients with underlying conditions (e.g., myasthenia gravis, amyotrophic lateral sclerosis) that predispose them

to these symptoms. The concomitant use of an aminoglycoside, muscle relaxant, or other agent that interferes with neuromuscular transmission may result in an increased response and should be closely monitored. Immediate medical attention may be required in patients who experience respiratory, speech, or swallowing difficulties.

The adverse events most often experienced with abobotulinumtoxinA in the clinical studies in patients with cervical dystonia included muscular weakness (16%), dysphagia (15%), dry mouth (13%), injection site discomfort (13%), fatigue (12%), headache (11%), musculoskeletal pain (7%), eye symptoms (7%), dysphonia (6%), and injection site pain (5%). In the treatment of glabellar lines, caution must be exercised when administering the drug in patients with surgical alterations to the facial anatomy, excessive weakness or atrophy in the target muscle, marked facial asymmetry, inflammation at the injection site, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or the inability to substantially lessen glabellar lines by physically spreading them apart.

The abobotulinumtoxinA formulation contains human albumin, the inclusion of which carries a remote risk for transmission of viral diseases and a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD). However, no cases of transmission of viral diseases or CJD have ever been reported for albumin. The formulation may also contain trace amounts of cow's milk protein, and patients who are known to be allergic to cow's milk protein should not be treated with abobotulinumtoxinA.

Approximately 3% of patients with cervical dystonia experience the development of binding or neutralizing antibodies as treatment with abobotulinumtoxinA is continued. However, the importance of this response has not been determined because some patients have continued to experience clinical benefit.

AbobotulinumtoxinA is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. Its effectiveness and safety in patients younger than 18 years have not been evaluated.

Because of the possibility of excessive systemic anticholinergic effects, caution must be exercised if medications having anticholinergic activity are used in patients treated with abobotulinumtoxinA.

The recommended initial dose of abobotulinumtoxinA for the treatment of cervical dystonia is 500 units administered intramuscularly as a divided dose among affected muscles. The peak effect occurs between 2 and 4 weeks after injection. Retreatment upon the return of symptoms should not occur in intervals of less than 12 weeks, and the dosage may be titrated in 250-unit steps between 250 and 1,000 units based on the patient's response.

For the treatment of glabellar lines, a total dose of 50 units, divided in five equal aliquots of 10 units each, should be administered to affected muscles. Retreatment should be administered no more frequently than every 3 months.

The potency units for abobotulinumtoxinA are specific to the drug and assay method used. Therefore, they are not the same as or interchangeable with other botulinum toxin

products.

AbobotulinumtoxinA is supplied in single-use vials containing 300 units and 500 units of the drug in a lyophilized form. The vials should be stored in a refrigerator. The contents of a vial containing 500 units should be reconstituted with 1 mL of 0.9% Sodium Chloride Injection without preservative to provide a solution of 500 units/mL. The contents of a vial containing 300 units should be reconstituted with 0.6 mL of 0.9% Sodium Chloride Injection without preservative to provide a solution with 250 units/0.5 mL. The vials should be gently swirled to dissolve the medication. A sterile 23- or 25-gauge needle should be used for administration of the solution into the affected muscles. If the solution is not administered promptly following reconstitution, it should be stored in a refrigerator and used within 4 hours.

Vials containing 300 units of the drug should be used for the treatment of glabellar lines, and the product labeling should be consulted for information regarding reconstitution and administration.

### **Antineoplastic agents**

Approximately 13,000 people die from complications of kidney cancer each year in the United States. Renal cell carcinoma is the most common type of kidney cancer, and if detected in time, a cure may be possible with surgical removal of the kidney. However, if surgery is not appropriate or if the cancer has metastasized, the prognosis is poor. Before 2006, only one drug, aldesleukin (Proleukin), which was first marketed in 1992, had been approved for the treatment of renal cell carcinoma. However, its effectiveness is limited, and many patients experience adverse events.

Since 2006, five new drugs and one previously marketed drug have been approved for the treatment of renal cell carcinoma, thereby extending the options for treating this disease considerably. Sunitinib (Sutent) and sorafenib (Nexavar) are multikinase inhibitors that were marketed in early 2006, and temsirolimus (Torisel) and everolimus (Afinitor) are inhibitors of mammalian target of rapamycin that were marketed in 2007 and 2009, respectively. Bevacizumab (Avastin) was initially approved for the treatment of colorectal cancer and more recently for additional indications including renal cell carcinoma, for which it is used in combination with interferon alfa.

### **Pazopanib hydrochloride**

Pazopanib hydrochloride (Votrient—GlaxoSmithKline) is a multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptors, as well as other growth factor receptors, and has properties that are most similar to those of sunitinib and sorafenib. It has been approved for the treatment of patients with advanced renal cell carcinoma. Pazopanib was evaluated in a placebo-controlled study in which progression-free survival averaged 9.2 months for patients receiving the drug compared with 4.2 months for those who did not receive the drug. It has not been directly compared in clinical studies with other medications that are used in the treatment of renal cell carcinoma.

A risk of hepatotoxicity, manifested as increases in serum transaminases (ALT and AST) and bilirubin, is an important concern with the use of pazopanib and is the subject of a boxed warning in its labeling. Hepatotoxicity may be severe and even fatal, and serum liver function tests should be determined before initiation of treatment and at least once every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Monitoring should be continued on a periodic basis thereafter. Based on changes in liver function tests, treatment should be reduced, interrupted, or discontinued.

Pazopanib has also been reported to cause prolongation of the QT interval of the electrocardiogram, and it should be used with caution in patients with a history of QT interval prolongation and/or other risk factors such as the concurrent use of other medications (e.g., antiarrhythmics, moxifloxacin [Avelox]) that also have this potential. Fatal hemorrhagic events have been experienced by patients treated with pazopanib, and it should not be used in patients with a history of hemoptysis, cerebral, or clinically significant gastrointestinal (GI) hemorrhage in the previous 6 months. Other important adverse events that require careful patient selection and monitoring included arterial thrombotic events, GI perforation or fistula, hypertension, hypothyroidism, and proteinuria. Because pazopanib and drugs that act similarly may impair wound healing, treatment should be stopped at least 7 days before scheduled surgery.

The adverse events experienced most frequently with the use of pazopanib in the clinical studies included diarrhea (52%), hypertension (40%), hair color changes (38%), nausea (26%), anorexia (22%), vomiting (21%), fatigue (19%), ALT increase (53%), AST increase (53%), glucose increase (41%), total bilirubin increase (36%), leukopenia (37%), neutropenia (34%), and thrombocytopenia (32%).

Pazopanib may cause fetal harm if used during pregnancy and is classified in Pregnancy Category D. Women of childbearing potential should be advised to avoid becoming pregnant. Whether the drug is excreted in human milk is not known, and a decision should be made to discontinue nursing or not use the drug. The effectiveness and safety of pazopanib in pediatric patients have not been established.

The bioavailability of pazopanib is significantly increased (i.e., increased area under the curve and a twofold increase in peak serum concentrations) if the tablets are crushed before administration and if the drug is administered with food. Because of the possibility of an inconsistent response from increased exposure, the tablets should not be crushed and the drug should be administered at least 1 hour before or 2 hours after a meal.

Pazopanib undergoes extensive metabolism, primarily via the CYP3A4 metabolic pathway and to a minor extent via the CYP1A2 and -2C8 pathways. Excretion occurs almost entirely via the feces, with renal elimination accounting for less than 5% of the administered dose. Clearance is substantially reduced in patients with hepatic impairment, and the drug is not recommended for use in patients with severe hepatic impairment.

The use of a strong CYP3A4 inhibitor (e.g., clarithromy-

cin, ketoconazole, ritonavir) should be expected to increase the concentration and activity of pazopanib, and concurrent use with one of these agents or with grapefruit juice should be avoided. If avoiding the use of the other medication is not possible, a reduction in dosage of pazopanib should be considered. The use of a strong CYP3A4 inducer such as rifampin will reduce the concentration and activity of pazopanib, and the new drug should not be used if chronic use of a strong CYP3A4 inducer cannot be avoided. The concomitant use of pazopanib with other medications that have narrow therapeutic windows and are substrates for the CYP3A4, -2D6, and/or -2C8 pathways is not recommended because of the potential for a greater risk of serious adverse events.

The recommended dosage of pazopanib is 800 mg once a day at least 1 hour before or 2 hours after a meal. If a dose is missed, it should not be administered if it is less than 12 hours until the next dose. A dosage of 200 mg once a day is recommended for patients with moderate hepatic impairment. If liver function test abnormalities occur during treatment, the product labeling should be consulted for the recommendations for dosage adjustment or interruption of therapy. When used in patients in whom it is also considered necessary to use a strong CYP3A4 inhibitor, the recommended dosage of pazopanib is 400 mg once a day, which may be reduced further if adverse events occur.

Pazopanib hydrochloride is supplied in tablets in amounts equivalent to 200 mg and 400 mg pazopanib base.

#### **Ofatumumab**

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia experienced by adults. It is a slowly progressing blood and bone marrow disease, and approximately 15,000 new cases are diagnosed in the United States each year. For many years, alkylating agents such as chlorambucil and cyclophosphamide represented the primary treatment, but these agents seldom provide a complete response. The purine nucleoside fludarabine is also effective in the treatment of CLL, as is the monoclonal antibody alemtuzumab (Campath), which was approved in 2001 for the treatment of patients with B-cell CLL who have been treated with alkylating agents and who have failed fludarabine therapy. In 2008, bendamustine (Treanda), an agent that exhibits actions characteristic of both an alkylating agent and a purine nucleoside, was approved for the treatment of CLL. In recent years, the value of rituximab (Rituxan) in the treatment of CLL has been recognized and its use in combination regimens has been reported to improve overall survival. This use has not been a labeled indication for rituximab, but in February 2010, FDA approved its use in combination with fludarabine and cyclophosphamide for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

The CD20 antigen is expressed on the surface of normal B-cells and on malignant B-cells in patients with CLL. Ofatumumab (Arzerra—GlaxoSmithKline) is a human monoclonal antibody that, like rituximab, binds to the CD20 antigen, although there are distinctions in the nature of the binding of the

two agents to CD20. The new drug was approved in late 2009 for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. Its effectiveness was demonstrated in a study in which 42% of the patients with CLL who were refractory to both fludarabine and alemtuzumab responded to treatment with ofatumumab. These patients had a median duration of response of 6.5 months. Ofatumumab has not been directly compared with rituximab in clinical studies.

Ofatumumab is administered via intravenous infusion, and many patients experience infusion reactions characterized by responses such as bronchospasm, dyspnea, laryngeal edema, pulmonary edema, flushing, hypotension, syncope, cardiac ischemia, back pain, abdominal pain, pyrexia, rash, and urticaria. In clinical studies, infusion reactions occurred in 44% of patients on the day of the first infusion, 29% on the day of the second infusion, and less frequently during subsequent infusions. The risk associated with these events warrants interruption of the infusion for reactions of any severity. Patients should receive premedication with acetaminophen, an antihistamine, and a corticosteroid.

Neutropenia usually occurs in patients treated with ofatumumab, and 42% of patients with normal neutrophil counts at baseline experienced this response at a grade 3 or 4 level of severity. Complete blood counts and platelet counts should be monitored at regular intervals during therapy, and the frequency of monitoring should be increased in patients who develop grade 3 or 4 cytopenias.

Other frequently experienced adverse events with the use of ofatumumab included pneumonia (23%), pyrexia (20%), cough (19%), diarrhea (18%), anemia (16%), fatigue (15%), dyspnea (14%), rash (14%), upper respiratory tract infection (11%), bronchitis (11%), and nausea (11%).

Patients treated with ofatumumab are at risk of several rare but very serious complications. Progressive multifocal leukoencephalopathy may occur, and this possibility should be considered in any patient with new onset of or changes in pre-existing neurological signs and symptoms. Obstruction of the small intestine may occur, and a diagnostic evaluation should be performed if obstruction is suspected.

Because of the potential for hepatitis B reactivation, patients at high risk of hepatitis B virus (HBV) infection should be screened before initiating treatment with ofatumumab. Carriers of HBV should be closely monitored for laboratory signs of active HBV infection during treatment with the new drug and for up to 12 months after the last infusion.

The use of live viral vaccines during or following the use of ofatumumab has not been evaluated, and these vaccines should not be administered to patients who have recently received the drug.

Ofatumumab is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. Its effectiveness and safety have not been evaluated in pediatric patients.

Prior to each dose of ofatumumab, patients should be premedicated with acetaminophen 1,000 mg, an oral or intravenous antihistamine (cetirizine 10 mg or equivalent), and an in-

travenous corticosteroid (prednisolone 100 mg or equivalent). The dosage of the corticosteroid should not be reduced for doses 1, 2, and 9 but may be reduced for the other doses based on the parameters identified in the product labeling.

Ofatumumab is administered via intravenous infusion and must not be administered as an intravenous push or bolus. Twelve doses of the drug are administered in a course of treatment in the following amounts and schedule: the initial dose of 300 mg (dose 1) is followed 1 week later by 2,000 mg weekly for seven doses (doses 2–8), followed 4 weeks later by 2,000 mg every 4 weeks for four doses (doses 9–12). The product labeling should be consulted for information regarding the rates of infusion and dosage/infusion rate modification if infusion reactions occur.

Ofatumumab is supplied in single-use vials containing 100 mg of the drug in a 5-mL volume. The vials should be stored in a refrigerator. Doses of the drug should be prepared in polyolefin bags containing 1,000 mL of 0.9% Sodium Chloride Injection. To prepare the 300-mg dose of ofatumumab, 15 mL of the diluent should be withdrawn from the bag and discarded. Then, 5 mL solution should be withdrawn from each of three vials of ofatumumab and added to the bag. The diluted solution should be mixed by gentle inversion but without shaking. To prepare a 2,000-mg dose of the drug, 100 mL of the diluent should be withdrawn from the bag and discarded. Then, 5 mL solution should be withdrawn from each of 20 vials of the drug and added to the bag.

The diluted solution should be administered using an infusion pump, the in-line filter provided with the product, and polyvinyl chloride administration sets. The intravenous line should be flushed with 0.9% Sodium Chloride Injection before and after each dose. The diluted solution should be stored in the refrigerator and the infusion started within 12 hours of preparation.

### **Pralatrexate**

Peripheral T-cell lymphoma (PTCL) is one of the non-Hodgkin's lymphomas and occurs in almost 10,000 patients each year in the United States. Most patients have been treated with cyclophosphamide, doxorubicin, vincristine, and prednisone or a similar regimen, but none of these agents has been specifically approved for the treatment of PTCL. Many patients are refractory to these regimens or experience relapses.

Pralatrexate (Folotylin—Allos) is a folate analog metabolic inhibitor that has properties that are most similar to those of methotrexate. It competitively inhibits dihydrofolate reductase and is the first drug to be approved for the treatment of PTCL. Pralatrexate is administered intravenously and is specifically indicated for the treatment of patients with relapsed or refractory PTCL. The new drug was approved based on the overall response rate in the clinical studies. However, clinical benefit such as an improvement in progression-free survival or overall survival has not been demonstrated. In the clinical study in which it was evaluated in patients with relapsed or refractory PTCL, the response rate was 27%, with approximately two-thirds of these patients experiencing a partial response.

The most frequently experienced adverse events associated with the use of pralatrexate in the clinical studies included mucositis (70%), thrombocytopenia (41%), nausea (40%), fatigue (36%), anemia (34%), constipation (33%), pyrexia (32%), edema (30%), cough (28%), epistaxis (26%), vomiting (25%), and neutropenia (24%).

Complete blood cell counts including platelets and the severity of mucositis should be monitored weekly. Before administering any dose of pralatrexate, the severity of mucositis should not exceed grade 1, the platelet count should be at least 100,000/mL for the first dose and at least 50,000/mL for all subsequent doses, and the absolute neutrophil count should be at least 1,000/mL. Patients should take folic acid and receive vitamin B12 to potentially reduce treatment-related mucositis and hematological toxicity.

Liver function test abnormalities have also been reported in patients treated with pralatrexate, and liver function should be monitored because of the possible need to adjust the dosage. The drug has not been evaluated in patients with renal impairment, and caution should be exercised when it is used in patients with moderate to severe renal impairment. Serum chemistry tests, including hepatic and renal function, should be performed before starting the first and fourth dose of a given cycle of treatment.

Pralatrexate may cause fetal harm if it is administered during pregnancy, and it is classified in Pregnancy Category D. Women of childbearing potential should be advised to avoid becoming pregnant. Although whether it is excreted in human milk is not known, a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of pralatrexate in pediatric patients have not been evaluated.

Approximately one-third of a dose of pralatrexate is excreted unchanged in the urine. The concurrent use of probenecid delays clearance that is associated with a corresponding increase in exposure to the new drug. Concomitant use of other drugs that are subject to substantial renal clearance (e.g., trimethoprim-sulfamethoxazole, NSAIDs) may delay the clearance of pralatrexate.

The recommended dosage of pralatrexate is 30 mg/m<sup>2</sup> administered as an intravenous push over 3 to 5 minutes via the side port of a free-flowing 0.9% Sodium Chloride Injection intravenous line once a week for 6 weeks in 7-week cycles until progressive disease or unacceptable toxicity. The occurrence of severe adverse events may require a reduction of dosage, omission of a dose, or interruption of therapy, and the product labeling should be consulted for the specific recommendations for dosage modification.

Pralatrexate is supplied in single-use vials that contain the drug in a concentration of 20 mg/mL in volumes of 1 mL (20 mg) and 2 mL (40 mg). The vials should be stored in a refrigerator. The solution should not be diluted prior to administration.

Supplementation with folic acid and vitamin B12 should be provided for patients being treated with pralatrexate. Folic acid in a dosage of 1 to 1.25 mg once a day should be initiated during the 10-day period preceding the first dose of pralatrexate and should be continued during the entire course of ther-

apy and for 30 days following the last dose. Patients should also receive vitamin B12 intramuscularly in a dose of 1 mg not more than 10 weeks before the first dose of pralatrexate and every 8 to 10 weeks thereafter. Subsequent injections may be given on the same day as when a dose of pralatrexate is to be administered.

### Agent for cryopyrin-associated periodic syndromes

Cryopyrin-associated periodic syndromes (CAPS) are a group of rare, inherited chronic inflammatory diseases that are characterized, in part, by symptoms such as recurrent rash, fever/chills, joint pain, fatigue, and eye pain/redness. CAPS include three related disorders classified as autoinflammatory diseases: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID). The incidence of CAPS is estimated to be approximately 1 in 1 million people in the United States.

The symptoms of FCAS are triggered by exposure to cooling temperatures. Its onset occurs during early childhood or adolescence and persists throughout the patient's life. MWS symptoms are triggered by random, unknown factors and possibly exercise, stress, or cold. MWS is often associated with hearing loss and/or amyloidosis—an accumulation of amyloid protein in organs such as the kidney. NOMID is characterized by major central nervous system complications. It is the most severe form of CAPS, and symptoms usually appear shortly after birth.

CAPS are generally caused by mutations in the *NLRP-3* (nucleotide-binding domain, leucine-rich family [NLR], pyrin domain containing 3) gene (also known as the *CIAS1* [cold-induced auto-inflammatory syndrome 1] gene), which encodes cryopyrin, a protein that regulates inflammation in the body. The mutation in the *NLRP-3* gene causes increased activity of cryopyrin, which causes an overproduction of interleukin (IL)-1 beta, resulting in an inflammatory response and the symptoms of CAPS. Most but not all patients with CAPS have the *NLRP-3* gene mutation.

In 2008, rilonacept (Arcalyst) was marketed as the first drug to be approved for the treatment of CAPS. It is an IL-1 blocker that is administered subcutaneously for the treatment of CAPS, including FCAS and MWS in adults and children 12 years of age or older.

**Canakinumab** (Ilaris—Novartis) is a human monoclonal anti-human IL-1 beta antibody that neutralizes the activity of IL-1 beta by blocking its interaction with IL-1 receptors. It is administered subcutaneously and is specifically indicated for the treatment of CAPS in adults and children 4 years of age or older, including FCAS and MWS. Neither rilonacept nor canakinumab has been evaluated to a considerable extent in patients with NOMID.

The effectiveness of canakinumab was demonstrated in a study in which a complete response was observed in 71% of patients 1 week after initiation of treatment and in 97% of patients by week 8. Patients achieving a complete clinical



response were randomized into a placebo-controlled withdrawal period as the second part of this study. A total of 81% of the patients randomized to placebo experienced a flare of the disease compared with none (0%) of the patients randomized to canakinumab. Serum amyloid A and C-reactive protein values, which are typically elevated in patients with CAPS with active disease, were also reduced.

The most frequently experienced adverse events with the use of canakinumab were nasopharyngitis (34%), diarrhea (20%), influenza (17%), rhinitis (17%), headache (14%), nausea (14%), vertigo (11%), and injection site reactions (9%). Because it inhibits IL-1, canakinumab may interfere with the immune response to infections. Treatment should not be initiated in patients with an active infection. If a patient already being treated with canakinumab develops a serious infection, therapy should be discontinued. An increased risk of infection exists if the new drug is used concurrently with a tumor necrosis factor blocker (adalimumab [Humira], certolizumab [Cimzia], etanercept [Enbrel], golimumab [Simponi], and infliximab [Remicade]) or the IL-1 blocker anakinra (Kineret), and concurrent use should be avoided. Live vaccines should not be administered to patients being treated with canakinumab, and patients should receive all recommended vaccinations before initiating treatment with the new agent.

The use of medications that cause immunosuppression may increase the risk of malignancies, and canakinumab should be considered to have this potential. Assays were performed to detect antibodies directed against canakinumab in patients in the clinical studies. However, none of the patients

tested positive for treatment-emergent binding antibodies at the time points tested.

Canakinumab is classified in Pregnancy Category C and should be used during pregnancy only if the anticipated benefit justifies the risk to the fetus. Its effectiveness and safety in children younger than 4 years have not been established, although the studies of its use in children 4 to 11 years of age provides an advantage over riloncept, which currently is not indicated for use in children younger than 12 years.

Like riloncept, canakinumab is administered subcutaneously. However, it only needs to be administered every 8 weeks, whereas riloncept is administered once a week. The recommended dosage of canakinumab is 150 mg every 8 weeks for patients weighing more than 40 kg. For patients with a body weight between 15 kg and 40 kg, the recommended dosage is 2 mg/kg every 8 weeks. For children with an inadequate response, the dosage may be increased to 3 mg/kg every 8 weeks.

Canakinumab is supplied in single-use vials containing 180 mg of the drug in a lyophilized powder form. The vials should be stored in a refrigerator. The contents of a vial should be reconstituted with 1 mL of preservative-free Sterile Water for Injection to provide a solution that contains 150 mg/mL. The vial should be slowly swirled at an angle of about 45° for approximately 1 minute and allowed to stand for 5 minutes. The vial should then be gently turned upside down and back again 10 times, then allowed to stand for approximately 15 minutes. If not administered within 60 minutes following reconstitution, the solution should be stored in a refrigerator and used within 4 hours.

#### **CPE Credit:**

To obtain 2.0 contact hours of continuing pharmacy education credit (0.2 CEUs) for "New therapeutic agents marketed in the second half of 2009: Part 2," go to [www.pharmacist.com](http://www.pharmacist.com) and take your test online for instant credit. CPE processing is free for APhA 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 April 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](http://www.pharmacist.com) no later than April 30, 2010.

1. **With the use of which of the following agents is it important to provide supplementation with folic acid and vitamin B12?**
  - a. Vigabatrin
  - b. Telavancin
  - c. Pazopanib
  - d. Pralatrexate
2. **Which of the following agents may be associated with swallowing and breathing difficulties?**
  - a. Canakinumab
  - b. AbobotulinumtoxinA
  - c. Ofatumumab
  - d. Pazopanib
3. **Which of the following agents may be associated with vision loss?**
  - a. Telavancin
  - b. Pralatrexate
  - c. Vigabatrin
  - d. Canakinumab
4. **Which of the following agents is known to interfere with coagulation tests?**
  - a. Telavancin
  - b. AbobotulinumtoxinA
  - c. Ofatumumab
  - d. Canakinumab
5. **The labeling for which of the following agents includes a boxed warning regarding the risk of hepatotoxicity?**
  - a. AbobotulinumtoxinA
  - b. Pazopanib
  - c. Ofatumumab
  - d. Telavancin
6. **Which of the following agents is most likely to be associated with the occurrence of mucositis?**
  - a. Pazopanib
  - b. Canakinumab
  - c. AbobotulinumtoxinA
  - d. Pralatrexate
7. **Which of the following agents is most likely to be associated with serious infusion reactions that necessitate the use of premedications?**
  - a. Pralatrexate
  - b. Canakinumab
  - c. Ofatumumab
  - d. AbobotulinumtoxinA
8. **With the use of which of the following agents should a woman of childbearing potential have a serum pregnancy test performed before administration?**
  - a. Vigabatrin
  - b. Ofatumumab
  - c. Canakinumab
  - d. Telavancin
9. **Which of the following agents is most likely to interact with cytochrome P450 (CYP)3A4 inhibitors and inducers?**
  - a. Pazopanib
  - b. Vigabatrin
  - c. Pralatrexate
  - d. Telavancin
10. **Which of the following agents acts as an inhibitor of interleukin-1 beta?**
  - a. Ofatumumab
  - b. Canakinumab
  - c. Pralatrexate
  - d. AbobotulinumtoxinA
11. **Which of the following statements is correct regarding telavancin?**
  - a. It is highly effective in the treatment of infections caused by vancomycin-resistant enterococci.
  - b. Its labeled indications include lower respiratory tract infections, skin infections, and meningitis.
  - c. Taste disturbance is a common adverse event.
  - d. Serum concentrations should be determined at least every 3 days.
12. **Which of the following statements is correct regarding telavancin?**
  - a. It should be administered by intravenous infusion over a period of 60 minutes.
  - b. Hearing loss is an important risk associated with its use.
  - c. It is extensively metabolized via the CYP3A4 pathway.
  - d. It is administered every 12 hours.
13. **Which of the following statements is correct regarding vigabatrin?**
  - a. It reduces the concentration of GABA in the central nervous system.
  - b. It is the first drug to be approved for the treatment of infantile spasms.
  - c. Serum concentrations should be closely monitored.
  - d. It undergoes extensive first-pass metabolism.

**14. Which of the following statements is correct regarding vigabatrin?**

- a. It acts as a serotonin and norepinephrine reuptake inhibitor.
- b. The consumption of grapefruit juice should be avoided.
- c. It must be administered apart from meals.
- d. It is administered twice a day.

**15. Which of the following statements is correct regarding abobotulinumtoxinA?**

- a. It provides its clinical benefit by acting as a cholinergic receptor agonist.
- b. Its labeled indications include cervical dystonia and fibromyalgia.
- c. It is administered at intervals of 12 weeks or longer.
- d. It is administered subcutaneously.

**16. Which of the following statements is correct regarding pazopanib?**

- a. It is a multi-tyrosine kinase inhibitor of vascular endothelial growth factor receptors.
- b. It is indicated for the treatment of chronic lymphocytic leukemia.
- c. It has been demonstrated in comparative studies to be more effective than sunitinib.
- d. It must be administered with food to obtain optimal absorption.

**17. Which of the following statements is correct regarding pazopanib?**

- a. It is indicated for use in combination with sorafenib.
- b. Its use has been associated with prolongation of the QT interval.
- c. It is eliminated in unchanged form in the urine.
- d. It is administered twice a day.

**18. Which of the following statements is correct regarding ofatumumab?**

- a. It acts by binding to the CD20 antigen on the surface of malignant B-cells.
- b. It is indicated for the treatment of refractory peripheral T-cell lymphoma.
- c. It has been demonstrated in comparative studies to be more effective than rituximab.
- d. A lower dosage should be used in patients with moderate to severe renal impairment.

**19. Which of the following statements is correct regarding pralatrexate?**

- a. It acts as a xanthine oxidase inhibitor.
- b. It is indicated for the treatment of advanced renal cell carcinoma.
- c. It is administered as an intravenous push injection.
- d. It is administered once a day.

**20. Which of the following statements is correct regarding canakinumab?**

- a. Its properties are most similar to those of etanercept.
- b. It is classified as a tumor necrosis factor blocker.
- c. It is administered intravenously.
- d. It is administered every 8 weeks.

**CPE Processing:**

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