

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

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Abstract

Objective: To provide information regarding the most important properties of new therapeutic agents marketed in the first 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: 16 new therapeutic agents were marketed in the United States during the first half of 2009. Eight of these agents were reviewed in the first article in this two-part series, and the other eight agents (including two in a combination product) are reviewed in this second part of the series: tolvaptan, degarelix acetate, everolimus, plerixafor, artemether/lumefantrine, besifloxacin hydrochloride, and benzyl alcohol. Indications and information on dosage and administration for these agents are reviewed, as are the most important pharmacokinetic properties, adverse events, drug interactions, and other precautions. Practical considerations for the use of the new agents are also discussed. When possible, the properties of the new drugs are compared with those of older drugs marketed for the same indications.

Conclusion: A number of the new drugs discussed in this second part of the series have properties and uses that provide significant advantages compared with older drugs. An understanding of the properties of these agents is important for the pharmacist to appropriately compare them with older agents used for the same conditions, 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.

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Part 1 of this series appeared in the September 2009 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 January to June 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

Agent for hyponatremia

Hyponatremia is generally defined as a serum concentration of less than 135 mEq/L. Sodium is the primary constituent of serum osmolality, and a normal serum concentration is essential for proper physiologic function. Patients with hyponatremia may be asymptomatic but, although considerable variation among individuals exists, symptoms are generally present when the serum sodium concentration decreases below 120 mEq/L. Neurologic symptoms may develop as a result of edema in the brain caused by fluid shifts and can range in severity from mild symptoms such as headache to more severe events such as confusion, seizures, paralysis, coma, and death.

Dilutional hyponatremia is the most common form of hyponatremia and occurs when total body water increases, thereby diluting serum sodium concentrations. The hormone arginine vasopressin (AVP), also known as antidiuretic hormone, regulates water loss from the body by altering water permeability of the renal collecting ducts, primarily by acting at V2 receptors. Excessive secretion of AVP can cause hyponatremia by inducing water retention by increasing free-water reabsorption from the renal collecting ducts, thereby diluting serum sodium. Dilutional hyponatremia may be further classified as euvolemic or hypervolemic, depending on the volume status of the patient. In euvolemic hyponatremia, total body water is slightly increased and the volume of the extracellular fluid (ECF) compartment is normal, whereas in hypervolemic hyponatremia, total body water is greatly increased and the ECF volume is expanded with associated edema and pitting. The concentration of AVP is usually elevated in both euvolemic and hypervolemic hyponatremia.

Hypervolemic hyponatremia is often associated with underlying conditions such as congestive heart failure, cirrhosis of the liver with ascites, nephrotic syndrome, and renal failure. Euvolemic hyponatremia is commonly associated with the syndrome of inappropriate antidiuretic hormone (SIADH), which is often present in endocrine and certain other disorders. Treatment of hyponatremia depends on factors such as the underlying cause of the sodium imbalance, volume status of the patient, the presence of symptoms, and the severity of symptoms. Conventional treatment options have included fluid restriction, hypertonic (3%) saline solution, diuretics, and selected other agents (e.g., demeclocycline, lithium). In 2006, conivaptan (Vaprisol) was marketed for treating euvolemic hyponatremia, and its indications were subsequently expanded to also include hypervolemic hyponatremia. Conivaptan is an AVP antagonist that acts primarily at V2 receptors but also has affinity for V1A receptors. Its action results in aquaresis, or excretion of free water. It is administered intravenously in hospitalized patients for a period of treatment that should not exceed 4 days.

Tolvaptan (Samsca—Otsuka) is a selective vasopressin V2 receptor antagonist that is administered orally. It is specifically indicated for treating clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure, cirrhosis, and SIADH. The effectiveness of the new drug was demonstrated in studies in which patients were treated for 30

days with tolvaptan or placebo. Serum sodium concentrations increased to a significantly greater degree in tolvaptan-treated patients as early as 8 hours after the first dose, and the change was maintained for 30 days. The percentage of patients needing fluid restriction was significantly less in the tolvaptan-treated group.

Tolvaptan has not been studied in patients in whom an urgent need exists to raise serum sodium acutely, and it is contraindicated in these patients. Its use is also contraindicated in patients who are anuric (for whom clinical benefit would not be expected) and in patients with hypovolemic hyponatremia. Because tolvaptan induces copious aquaresis, which is normally partially offset by fluid intake, dehydration and hypovolemia may occur. This risk is greater in potentially volume-depleted patients receiving diuretics or those who are fluid restricted.

The most important risk associated with the use of tolvaptan is too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours), which may cause osmotic demyelination syndrome resulting in dysarthria, dysphagia, lethargy, spastic quadriparesis, seizures, coma, and death. This is the subject of a boxed warning in the product labeling directing that treatment with tolvaptan be initiated and reinitiated only in a hospital where serum sodium concentrations may be closely monitored. Fluid restriction during the first 24 hours of treatment with tolvaptan may increase the likelihood of overly rapid correction of hyponatremia and should generally be avoided. The new agent is contraindicated in patients who are unable to sense or appropriately respond to thirst because of an increased risk of an overly rapid correction of serum sodium.

The adverse events most often reported in the clinical studies of tolvaptan include thirst (16%), dry mouth (13%), pollakiuria (extraordinary urinary frequency) or polyuria (11%), asthenia (9%), constipation (7%), and hyperglycemia (6%). Gastrointestinal bleeding was experienced by 10% of the patients with cirrhosis who were being treated for hyponatremia.

The acute reduction of the ECF volume associated with the use of tolvaptan may result in increased serum potassium concentrations. These concentrations should be monitored after initiation of treatment with the new drug in patients with a serum potassium greater than 5 mEq/L, as well as in those also being treated with medications known to increase serum potassium concentrations (e.g., potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers). When tolvaptan was used in patients who were being treated with another agent that increases serum potassium, the incidence of hyperkalemia was approximately 1 to 2% higher.

Tolvaptan is classified in Pregnancy Category C. Although whether it is excreted in human milk is not known, a decision should be made to discontinue nursing or not use the drug. The effectiveness and safety of tolvaptan in pediatric patients have not been established.

The absolute bioavailability of tolvaptan is not known, but at least 40% of a dose is absorbed and peak concentrations observed 2 to 4 hours after administration. The drug is extensively metabolized via the cytochrome P450 (CYP)3A metabolic pathways and eliminated entirely via nonrenal routes. Dosage ad-

Table 1. New therapeutic agents marketed in the United States from January to June 2009^a

Generic name	Trade name	Manufacturer	Therapeutic classification	Route of administration	FDA classification ^b
Artemether/lumefantrine	Coartem	Novartis	Antiparasitic agents	Oral	1-P, O
Besifloxacin hydrochloride	Besivance	Bausch and Lomb	Antibacterial agent	Ophthalmic	1-S
Benzyl alcohol	Ulesfia	Sciele	Pediculicide	Topical	1-S
Degarelix acetate	Firmagon	Ferring	Antineoplastic agent	Subcutaneous	1-S
Everolimus	Afinitor	Novartis	Antineoplastic agent	Oral	1-P
Plerixafor	Mozobil	Genzyme	Hematopoietic stem cell mobilizer	Subcutaneous	1-P, O
Tolvaptan	Samsca	Otsuka	Agent for hyponatremia	Oral	1-S

^aAdditional agents marketed during this time period are considered in part 1 of this two-part series.

^bFDA classification of new drugs: 1 = new molecular entity; O = designated orphan drug; P = priority review; S = standard review.

justment is not necessary in patients with hepatic and/or renal impairment, although the drug would not be effective in patients who are anuric.

The exposure to tolvaptan is markedly increased by strong CYP3A inhibitors (e.g., ketoconazole [e.g., Nizoral], itraconazole [e.g., Sporanox], clarithromycin [e.g., Biaxin], telithromycin [Ketek], indinavir [Crixivan], nelfinavir [Viracept], ritonavir [Norvir], saquinavir [Invirase]), and concurrent use is contraindicated. A substantial increase in exposure to tolvaptan should also be anticipated with the use of a moderate CYP3A inhibitor (e.g., fluconazole [e.g., Diflucan], erythromycin, diltiazem [e.g., Cardizem], verapamil [e.g., Calan], aprepitant [Emend]), and concurrent use should generally be avoided. The consumption of grapefruit juice has also been reported to increase exposure to tolvaptan, and patients should be advised to not drink this beverage during treatment.

Conversely, the exposure to tolvaptan may be substantially reduced by CYP3A inducers (e.g., rifampin [e.g., Rifadin], barbiturates, carbamazepine [e.g., Tegretol], phenytoin [e.g., Dilantin], St. John's wort), and concurrent use may necessitate an increase in dosage of the new drug.

Tolvaptan is both a substrate and inhibitor of P-glycoprotein (P-gp). When used concurrently with a P-gp inhibitor such as cyclosporine (e.g., Neoral), a reduction in dosage of tolvaptan may be necessary. The concurrent use of tolvaptan and digoxin, a P-gp substrate, has been reported to result in a 1.3-fold increase in the exposure to digoxin.

Initiation or reinitiation of treatment with tolvaptan should be done in a hospital so that the response to therapy and the risk of complications may be closely monitored. The usual initial dosage is 15 mg once a day. After at least 24 hours, the dosage may be increased to 30 mg once a day and, as needed, to a maximum of 60 mg once a day. During initiation and dosage titration, patients should be frequently monitored for changes in serum electrolytes and volume and for neurologic status. Fluid restriction should be avoided during the first 24 hours of therapy, and patients should be advised that they can continue ingestion of fluid in response to thirst. When tolvaptan treatment is discontinued, patients should be advised to resume fluid restriction and should be monitored for changes in serum sodium and volume status. Tolvaptan tablets are supplied in 15- and 30-mg potencies.

Antineoplastic agents

Degarelix acetate

Prostate cancer is androgen sensitive and responds to treatment that counteracts the effect of androgen and/or removes the source of androgen (surgical castration [i.e., orchiectomy]). Therefore, the primary goal of treatment is to reduce testosterone concentrations, and medications that act on gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone (LHRH), have been used for this purpose.

GnRH agonists (leuprolide [e.g., Lupron], goserelin [Zoladex], triptorelin [Trelstar]), with or without an antiandrogen (e.g., bicalutamide [Casodex]), have been effective in the treatment of many patients with prostate cancer. However, these agents cause an initial increase/surge in testosterone concentrations before the considerable reduction occurs. Some men, particularly those with advanced prostate cancer that also involves bones, the bladder, and spinal area, are not able to tolerate the initial testosterone surges.

In 2004, abarelix (Plenaxis) was marketed for treating advanced symptomatic prostate cancer in men for whom GnRH agonist treatment is not appropriate and who refuse surgical castration. This agent is a GnRH antagonist that directly blocks GnRH receptors in the pituitary, thereby reducing the secretion of testosterone without causing an initial increase in testosterone concentrations. However, abarelix is associated with a risk of serious allergic reactions and other restrictions to its use and is no longer marketed in the United States.

Degarelix acetate (Firmagon—Ferring) is a synthetic decapeptide amide that acts as a GnRH receptor antagonist. It binds reversibly to the pituitary GnRH receptors, thereby reducing the release of gonadotropins and consequently testosterone. Its properties are generally similar to those of abarelix, but its use has not been associated with serious allergic reactions and its indication and use are not restricted, as was the situation with abarelix. Approval of a trade name for degarelix was delayed initially; therefore, the drug was first marketed using its generic name. In early August, FDA approved the trade name Firmagon.

Degarelix is administered subcutaneously and is indicated for treating patients with advanced prostate cancer. Its effec-

tiveness has been demonstrated in clinical studies in which it was compared with leuprolide (7.5 mg I.M. once a month) for a period of 12 months. The primary endpoint was the reduction of serum testosterone concentrations to castration levels (≤ 50 ng/dL), and this was attained in 97% of patients treated with degarelix and 96% of the patients treated with leuprolide, resulting in the conclusion that degarelix is noninferior to leuprolide. The reduction of testosterone concentrations occurred much more quickly with degarelix, with 96% of patients attaining the endpoint within 3 days after the first monthly dose. After 14 days, 99% of the patients treated with degarelix attained the endpoint compared with 18% of those treated with leuprolide. However, after 28 days, 100% of the patients in both groups had attained the endpoint, and this response was maintained in almost all patients for the 12-month period of the study.

The therapeutic effect of degarelix should be monitored by measuring serum concentrations of prostate-specific antigen (PSA) periodically. If PSA increases, serum testosterone concentrations should be determined.

The adverse events most often experienced in the studies with degarelix (and the incidences with the new drug and leuprolide, respectively) include injection site reactions (e.g., pain, erythema, swelling, induration, nodule; 35%, <1%), hot flashes (26%, 21%), increased weight (9%, 12%), hypertension (6%, 4%), back pain (6%, 8%), arthralgia (5%, 9%), urinary tract infection (5%, 9%), chills (5%, 0%), constipation (5%, 5%), fatigue (3%, 6%), and increases in serum concentrations of transaminases and gamma-glutamyltransferase (10%; 5%). Because the use of degarelix results in suppression of the pituitary gonadal system, the results of diagnostic tests of the pituitary gonadotropic and gonadal functions conducted during and after degarelix treatment may be affected.

Long-term androgen deprivation therapy prolongs the QT interval of the electrocardiogram, and caution must be observed if degarelix is used in patients with congenital long QT syndrome, electrolyte abnormalities, or congestive heart failure or in patients being treated with other medications that prolong the QT interval (e.g., certain antidysrhythmic agents [e.g., quinidine, procainamide, amiodarone, sotalol]).

Degarelix is not indicated for use in women or children. However, a potential exists for it to be used off label in women. The drug may cause fetal harm if used during pregnancy. It is classified in Pregnancy Category X and is contraindicated in women who are or may become pregnant. Degarelix should not be used in nursing mothers, and a decision should be made whether to discontinue nursing or not use the drug.

Following subcutaneous administration, degarelix forms a depot at the injection site from which the drug is released to the circulation. The maximum serum concentration typically occurs within 2 days after administration, and the very slow release of the drug from the depot results in a median terminal half-life of approximately 53 days. Degarelix is subject to peptide hydrolysis during its passage in the hepatobiliary system, and is mainly excreted as peptide fragments in the feces. Approximately 20% to 30% of a dose is excreted unchanged in the urine. Information regarding the use of the drug in patients with

impaired renal function is limited, and the drug should be used with caution in patients with a creatinine clearance less than 50 mL/minute. Caution must also be exercised when degarelix is used in patients with severe hepatic impairment.

The initial dose of degarelix is 240 mg given as two deep subcutaneous injections of 120 mg at a concentration of 40 mg/mL. The maintenance dosage is 80 mg every 28 days, given as one subcutaneous injection at a concentration of 20 mg/mL. The first maintenance dose is given 28 days after the initial dose. Injections should be administered in the abdominal region, but the specific injection sites in this area should vary periodically and should be at sites in the abdomen that are not exposed to pressure (e.g., close to a waistband or belt) or close to the ribs.

Degarelix acetate is supplied as a lyophilized powder in vials containing 80 and 120 mg of the drug. The reconstitution and administration procedures should be performed while keeping the vials vertical at all times, and by gently swirling the vials when the diluent is added but not shaking the vials so as to prevent the formation of foam. The reconstituted drug must be administered within 1 hour after the addition of the diluent.

A Treatment Initiation pack contains two vials (each containing 120 mg of the drug) that are prepared for two subcutaneous injections. Each of the two vials should be reconstituted with 3 mL Sterile Water for Injection, a procedure that may take up to 15 minutes. For each of the two subcutaneous injections comprising the initial dose of degarelix, 3 mL solution (40 mg/mL) should be withdrawn from each vial without turning the vials upside down. The two injections should be administered at different sites in the abdomen.

A Treatment Maintenance pack of degarelix contains one vial with 80 mg of the drug. The powder is reconstituted with 4.2 mL Sterile Water for Injection. A volume of 4 mL is withdrawn from the vial to administer a dose of 80 mg (20 mg/mL) as a single subcutaneous injection.

Everolimus

Approximately 13,000 people died from complications of kidney cancer last 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. In 1992, aldesleukin (Proleukin) was marketed as the first drug to be approved for the treatment of renal cell carcinoma. However, its effectiveness is limited, and many patients experience serious adverse events.

Almost 15 years elapsed before another drug was approved for treating renal cell carcinoma, then three drugs were approved for this condition in a period of approximately 18 months. Sunitinib (Sutent) and sorafenib (Nexavar) are multikinase inhibitors that were marketed in early 2006, and temsirolimus (Torisel) was marketed in mid-2007. The principal active metabolite of temsirolimus is sirolimus (Rapamune), an immunosuppressant that was initially marketed in 1999 for prophylaxis of organ rejection in patients receiving transplants. Sirolimus, which is also known as rapamycin, inhibits the activation of mammalian target of rapamycin (mTOR), a kinase that

regulates cell proliferation, cell growth, and cell survival.

Everolimus (Afinitor—Novartis) is an mTOR inhibitor that binds to an intracellular protein, resulting in an inhibitory complex formation and inhibition of mTOR kinase activity. Its properties are most similar to those of temsirolimus. Although everolimus is the drug component of a drug-eluting stent (Xcience) that was marketed in 2008, that product is considered a device. Therefore, when it was approved for treating renal cell carcinoma in early 2009, this was its first approval in the United States for use as a drug, thereby qualifying it as a “new drug.”

The specific indication for everolimus is the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib. The new drug is administered orally, as are sunitinib and sorafenib, whereas temsirolimus is administered intravenously. The effectiveness of everolimus was demonstrated in studies in patients whose disease had worsened despite previous treatment with sunitinib, sorafenib, or both sequentially. The median progression-free survival was 4.9 months in the group of patients treated with everolimus plus best supportive care compared with 1.9 months in patients receiving placebo plus best supportive care.

There has been limited experience with using everolimus in a combination regimen with sorafenib or bevacizumab (Avastin) in patients with advanced renal cell carcinoma, and the new agent is also used to prevent rejection of organ transplants in some other countries. However, these are not labeled indications in the United States at the present time.

The most frequently experienced adverse event with the use of everolimus is oral ulceration (44%), including mouth ulcers, stomatitis, or oral mucositis. Topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided because they may exacerbate the condition.

Because everolimus has immunosuppressant properties, many patients (37%) experience infections, some of which have the potential to be fatal. Patients should be advised to promptly report a temperature of 100.5°F or more, chills, or other signs of infection, and appropriate treatment should be initiated. The use of live vaccines (e.g., intranasal influenza, measles, mumps, rubella, varicella), as well as close contact with those who have received live vaccines, should be avoided during treatment with everolimus.

The occurrence of noninfectious pneumonitis has been associated with the rapamycin derivatives and was experienced by 14% of those treated with everolimus. This possibility should be considered in patients who experience cough (30%), dyspnea (24%), or other respiratory signs and symptoms as serious complications could result. Therapy may need to be interrupted or discontinued, and using corticosteroids may be necessary.

Other adverse events that have been frequently attributed to the use of everolimus include asthenia (33%), fatigue (30%), diarrhea (30%), nausea (26%), vomiting (20%), rash (29%), peripheral edema (25%), anorexia (25%), and pyrexia (20%). Laboratory abnormalities reported at an incidence of 50% or higher include anemia (92%), lymphopenia (51%), hypercho-

lesterolemia (77%), hypertriglyceridemia (73%), hyperglycemia (57%), and increased creatinine (50%). Renal function, blood glucose, lipids, and hematologic parameters should be determined before initiating treatment and periodically thereafter. The use of everolimus is contraindicated in patients with a history of hypersensitivity to any of the rapamycin derivatives.

Everolimus may cause fetal harm if administered during pregnancy, and it is classified in Pregnancy Category D. Women of childbearing potential should use an effective method of contraception while being treated with the new drug and for up to 8 weeks following discontinuation of treatment. Although whether everolimus is excreted in human milk is unknown, a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of everolimus in pediatric patients have not been established.

Following oral administration, peak everolimus concentrations are reached in 1 to 2 hours. It is a substrate of CYP3A4 and P-gp and is extensively metabolized. Approximately 80% of the drug (as metabolites) is eliminated in the feces and only a small percentage in the urine. A reduction in dosage is recommended in patients with moderate hepatic impairment, but the drug is not recommended for use in patients with severe hepatic impairment. Dosage adjustment is not necessary in patients with renal impairment.

The exposure of everolimus may be significantly increased by the concurrent use of strong (e.g., clarithromycin [e.g., Bixxin]) or moderate (e.g., diltiazem [e.g., Cardizem]) inhibitors of the CYP3A4 and P-gp metabolic pathways, and the use of these agents in patients treated with the new drug should be avoided. Conversely, exposure to everolimus may be reduced by the concurrent use of a strong CYP3A4 inducer (e.g., rifampin [e.g., Rifadin], carbamazepine [e.g., Tegretol]), thereby necessitating an increase in dosage of everolimus.

The recommended dosage of everolimus is 10 mg once a day at the same time every day. The tablets should be swallowed whole and should not be chewed or crushed. In patients with moderate hepatic impairment, the recommended dosage is 5 mg once a day. This reduced dosage should also be considered in patients experiencing intolerable adverse events with the 10-mg dosage. In patients also being treated with a strong CYP3A4 inducer, an increase in dosage to 20 mg once a day (in 5-mg increments) should be considered.

Everolimus tablets are supplied in 5- and 10-mg potencies. The drug is available only through a restricted distribution program from ASD Healthcare (1-800-746-6273).

Hematopoietic stem cell mobilizer

Certain blood cancers such as multiple myeloma and non-Hodgkin's lymphomas are often treated with chemotherapy and/or radiation therapy. Although these treatments are among the most effective, their action is not selective and they destroy normal cells as well as cancer cells. The use of bone marrow transplants in the treatment of these cancers has permitted the use of dosages of chemotherapy and radiotherapy that are higher than those that would ordinarily be considered safe to use.

Hematopoietic stem cells mature into blood cells such as

red blood cells, white blood cells, and platelets. These stem cells are primarily located in the bone marrow, the greatest source of which is the bones of the hip and chest. Stem cells that leave the bone marrow and circulate into the blood are called peripheral blood stem cells (PBSCs). However, usually very few PBSCs exist in the blood because of the extent to which the stem cells bind to, or are anchored by, the bone marrow.

A surgical procedure designated as a bone marrow harvest was the first method used to extract marrow and stem cells that would be used for transplantation. More recently, stem cells have been collected from peripheral blood containing a much greater number of stem cells as a result of using medications that mobilize their transfer from the bone marrow. An autologous stem cell transplant is one in which a patient's own stem cells are used in the transplant.

The goals of a mobilization regimen include mobilizing enough stem cells for transplant; collecting stem cells that allow quick and long-lasting recovery of red blood cells, white blood cells, and platelets when they are reinfused; and minimizing the number of days that a patient is on the machine for apheresis (the process of collecting blood from a donor, removing one or more components, and then returning the remaining blood to the donor through transfusion). Following the collection of the stem cells, they are preserved, frozen, and stored until the time of transplant, when they are reinfused following the administration of high-dose chemotherapy or radiation. This enables patients to produce new cells to replace those destroyed during treatment.

Medications already on the market that have been used to mobilize the transfer of hematopoietic stem cells from the bone marrow to the peripheral blood include granulocyte colony-stimulating factor (G-CSF; filgrastim [Neupogen]) and granulocyte-macrophage colony-stimulating factor (sargramostim [Leukine]). In 2009, the hematopoietic stem cell mobilizer **plerixafor** (Mozobil—Genzyme) was marketed. The new drug is administered subcutaneously and is specifically indicated for use in combination with G-CSF to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma. Plerixafor is an inhibitor of CXCR4 chemokine receptors. Stem cell CXCR4 has a role in anchoring these cells to the marrow matrix, and when it is inhibited, more stem cells are transferred to peripheral blood for collection during apheresis.

CXCR4 is a coreceptor for the human immunodeficiency virus (HIV), but limited use of plerixafor in patients with HIV infection did not demonstrate sufficient benefit to warrant further investigation of this potential use.

The effectiveness of plerixafor was demonstrated in two studies in which patients received G-CSF and either plerixafor or placebo. In one study in patients with non-Hodgkin's lymphoma, 59% of the patients receiving plerixafor and G-CSF collected at least 5×10^6 CD34+ cells per kg from the peripheral blood in four or fewer apheresis sessions (median 3 days) compared with 20% of the patients receiving placebo and G-CSF.

In a study in patients with multiple myeloma, 72% of the patients receiving plerixafor and G-CSF collected at least 6×10^6 CD34+ cells per kg from the peripheral blood in two or fewer apheresis sessions compared with 34% of the patients who were mobilized with placebo and G-CSF.

Plerixafor should not be used in patients with leukemia because it may cause mobilization of leukemic cells and subsequent contamination of the apheresis product. The use of plerixafor and G-CSF has the potential for releasing tumor cells from the marrow that are collected in the apheresis product. However, studies of the effect of reinfusion of tumor cells are limited. Increased circulating leukocytes and decreased platelet counts have been reported with the use of plerixafor, and these hematologic parameters should be monitored.

The use of large doses of plerixafor in animal studies has been associated with enlargement of the spleen. Although this possibility was not specifically evaluated in the clinical studies, patients who report left upper abdominal pain and/or scapular or shoulder pain should be evaluated for splenic integrity.

The most frequently reported adverse events attributable to plerixafor include diarrhea (37%), nausea (34%), injection site reactions (34%), dizziness (11%), and vomiting (10%). Fatigue (27%) and headache (22%) were also frequently experienced but at an incidence that was similar to those receiving placebo and G-CSF. Vasovagal reactions, orthostatic hypotension, and/or syncope can occur following injection.

Plerixafor is teratogenic in animals and is classified in Pregnancy Category D. Women of childbearing potential should be advised to use effective contraceptive methods. Although whether it is excreted in human milk is unknown, a decision should be made whether to discontinue nursing or not use the drug. The effectiveness and safety of plerixafor in pediatric patients have not been established.

Following subcutaneous administration, peak plasma concentrations of plerixafor occur in approximately 30 to 60 minutes, and peak mobilization of CD34+ cells is observed between 6 and 9 hours. The major route of elimination is renal and clearance is reduced in patients with renal impairment.

Patients who are to be treated with plerixafor should first receive daily morning doses of G-CSF (10 μ g/kg) for 4 days prior to the first evening dose of plerixafor and on each day prior to apheresis. Plerixafor is administered in the evening approximately 11 hours before initiating apheresis for up to 4 consecutive days. The recommended dosage of plerixafor is 0.24 mg per kg body weight. The dosage is calculated based on actual body weight in patients up to 175% of ideal body weight. Exposure to the drug is increased with increased body weight, and the dosage of plerixafor should not exceed 40 mg a day. In patients with moderate and severe renal impairment (creatinine clearance ≤ 50 mL/minute), the dosage should be reduced to 0.16 mg per kg once a day, with a maximum dosage of 27 mg once a day.

Plerixafor is supplied in single-use vials containing 1.2 mL of a solution of the drug in a 20 mg/mL concentration. Any unused drug remaining after an injection must be discarded.

Antiparasitic agents

An estimated 350 to 500 million new cases of malaria develop worldwide each year, and approximately 1 million of these patients, mostly young children, die of complications of the disease. Malaria is caused by four species of the parasite *Plasmodium*, of which the most dangerous is *Plasmodium falciparum*. The effectiveness of chloroquine (e.g., Aralen) and certain other antimalarial drugs for the treatment and prophylaxis of malaria has declined significantly because of the extent to which strains of *P. falciparum* have become resistant to these agents. In response to the growing concerns about resistance to antimalarial agents, the World Health Organization recommends that countries in which resistance is a problem should use combination regimens, preferably those containing artemisinin derivatives (artemisinin-based combination therapies [ACTs]) for the treatment of malaria caused by *P. falciparum*.

The artemisinins are derived from the leaves of the *Artemisia annua* plant (wormwood), which has been used in traditional Chinese medicine for many centuries for treating fever. Specific derivatives that have been identified include artemether, arteether, artesunate, as well as an active metabolite, dihydroartemisinin (DHA). Although these derivatives are highly active against *P. falciparum*, they have a short elimination half-life that may contribute to a greater likelihood of relapse and/or faster emergence of resistance if they are used as monotherapy. Accordingly, their use in combination with other antimalarial agents that have a different mechanism of action has been encouraged.

Artemether and lumefantrine are new antimalarial drugs that have been marketed in an orally administered combination product having the trade name Coartem (Novartis). They are not marketed as individual agents in the United States. Artemether is converted to an active metabolite, DHA, and their activity has been attributed to the endoperoxide moiety. Lumefantrine is related to halofantrine (Halfan), which is an antimalarial agent that is no longer marketed in the United States. Both artemether and lumefantrine are active against the erythrocytic stages of *P. falciparum*. Whereas artemether and DHA have an elimination half-life of approximately 2 hours, lumefantrine has a long terminal half-life of 3 to 6 days.

Artemether/lumefantrine are indicated for the treatment of acute, uncomplicated malaria infections caused by *P. falciparum* in patients weighing 5 kg or more. The new product is not indicated for the treatment of severe malaria, for which intravenously administered antimalarial agents would be used, and is not indicated for preventing malaria.

The effectiveness of artemether/lumefantrine has been demonstrated in studies in geographical regions (e.g., Thailand, Africa) in which resistance to agents such as chloroquine has been an important problem. Six doses of the combination product are administered over a 3-day period. The 28-day cure rate, defined as clearance of the erythrocytic stage within 7 days without recrudescence by day 28, was more than 95% in most studies. In six studies with similar parameters, the median parasite clearance time ranged from 24 to 44 hours and the median fever clearance time ranged from 8 to 37 hours.

Compared with many other countries, malaria is reported infrequently in the United States, although the incidence is rising with the increase in international travel. Artemether/lumefantrine and other ACTs are currently used extensively on a worldwide basis, and the approval of this combination in the United States provides an important option for the treatment of malaria.

The effectiveness of artemether/lumefantrine in the treatment of mixed infections caused by *P. falciparum* and *P. vivax* has been evaluated in a study in 43 patients. All patients experienced clearing of their parasitemia within 48 hours, but parasite relapse occurred in approximately one-third of the patients. The explanation for this high rate of relapse is that artemether/lumefantrine are only active against the erythrocytic stage of *P. vivax* malaria and not against the forms of the parasite that exist in the liver and are the cause of subsequent relapse.

The most important concern with the use of artemether/lumefantrine is prolongation of the QT interval of the electrocardiogram and the resultant increased risk of cardiac dysrhythmias. The new agents should be avoided in patients with long QT syndrome or other conditions (e.g., clinically relevant bradycardia) known to prolong the QT interval, patients with a family history of congenital prolongation of the QT interval or sudden death, patients with hypokalemia or hypomagnesemia, and patients receiving other medications that prolong the QT interval (e.g., certain antidysrhythmic agents [e.g., quinidine, procainamide, amiodarone, sotalol], certain antipsychotic agents [e.g., pimozide, ziprasidone (Geodon)], certain antimicrobial agents [e.g., moxifloxacin (Avelox)]). Lumefantrine may inhibit the CYP2D6 metabolic pathway, and the use of the new product should be avoided in patients receiving medications that are metabolized via this pathway and have cardiac effects (e.g., flecainide [Tambocor], amitriptyline).

Because insufficient safety data exist, other antimalarial agents should not be used concurrently with artemether/lumefantrine unless other treatment options are not available. Halofantrine, quinine, and quinidine may also prolong the QT interval, and because of the long half-life of lumefantrine, a risk of an additive effect on the QT interval exists even when the drugs are used sequentially. Caution must be exercised if quinine or quinidine is used following artemether/lumefantrine, and halofantrine and the new product should not be used within 1 month of each other.

The adverse events experienced most frequently by adult patients in the clinical studies of artemether/lumefantrine included headache (56%), anorexia (40%), dizziness (39%), asthenia (38%), arthralgia (34%), myalgia (32%), nausea (26%), and pyrexia (25%). In children (≤ 16 years), the adverse events reported most often included pyrexia (29%), cough (23%), vomiting (18%), headache (13%), and anorexia (13%). Reports of hypersensitivity reactions, including urticaria, angioedema, and serious dermatological reactions, have been reported infrequently. The new product is contraindicated in patients who are known to be hypersensitive to any of its components.

The combination of artemether and lumefantrine is classified in Pregnancy Category C. Whether these agents are excreted

ed in human milk is unknown, and discontinuation of nursing an infant should be considered. The effectiveness and safety of the new product have been demonstrated in children 2 months of age or older with a body weight of 5 kg or more. This experience in pediatric patients is of particular importance in view of the vulnerability of children to serious complications of malaria.

Food, particularly a high-fat meal, increases the absorption and bioavailability of both artemether and lumefantrine considerably. Although patients with malaria often do not tolerate food well, and anorexia, nausea, and vomiting may occur as adverse events, the product should be administered with food (e.g., milk, broth, porridge, pudding, infant formula) as soon as it can be tolerated.

Both artemether and lumefantrine are primarily metabolized via the CYP3A4 pathway—the former agent to the active metabolite DHA and the latter agent to a metabolite that has very limited systemic exposure. Caution must be observed when the new agents are used concurrently with other medications that are substrates, inhibitors, or inducers of CYP3A4. Pharmacokinetic studies have not been conducted in patients with either hepatic or renal impairment, and dosage adjustment is not necessary in patients with mild to moderate hepatic or renal impairment. Caution must be exercised when the new agents are used in patients with severe hepatic or renal impairment.

Antiretroviral agents, particularly protease inhibitors and nonnucleoside reverse transcriptase inhibitors, have variable patterns of inhibition, induction, or competition for CYP3A4. The result of concurrent use with artemether/lumefantrine may be an increase in lumefantrine concentrations with associated increased potential for QT prolongation, a decrease in the concentrations of artemether and lumefantrine resulting in a reduction in antimalarial efficacy, or a decrease in the concentrations of the antiretroviral agents resulting in a reduction in efficacy. Concomitant therapy must be closely monitored.

The concurrent use of ketoconazole (e.g., Nizoral), a potent CYP3A4 inhibitor, has been reported to increase exposure to artemether, DHA, and lumefantrine. Adjusting the dosage of artemether/lumefantrine is not considered necessary when a potent CYP3A4 is used concurrently. However, the increased risk of QT prolongation resulting from increased lumefantrine concentrations should be closely monitored.

Artemether induces CYP3A4, and one consequence may be a reduction in the activity of hormonal contraceptives that are metabolized via this pathway. Patients using hormonal contraceptives should be advised to use an additional nonhormonal method of birth control.

The use of artemether/lumefantrine soon after the use of mefloquine (e.g., Lariam) has been reported to decrease exposure to lumefantrine, possibly as a result of reduced absorption secondary to a mefloquine-induced decrease in bile production. This could result in decreased antimalarial efficacy, and the consumption of food with doses of the new product is even more important.

Coartem tablets are scored and contain 20 mg artemether and 120 mg lumefantrine. Doses should be administered with food, and six doses are given during a 3-day period. For infants,

children, and other patients who are unable to swallow tablets, the tablets may be crushed and mixed with one to two teaspoons of water immediately before administering the drugs. If a patient experiences vomiting within 1 to 2 hours of administration, a repeat dose should be given.

The initial dose of artemether/lumefantrine, followed by the second dose 8 hours later, should be administered on the first day of treatment. Subsequent doses should be administered in the morning and evening of the second and third days for a total of six doses. The number of tablets to be administered per dose is four tablets for patients weighing 35 kg or more, three tablets for those weighing 25 kg to less than 35 kg, two tablets for those weighing 15 kg to less than 25 kg, and one tablet for those weighing 5 kg to less than 15 kg.

Antibacterial agent

Bacterial conjunctivitis, often referred to as “pink eye,” is one of the most common eye infections and is characterized by irritation and redness of the eye, as well as a discharge. The infection is contagious and usually persists for 7 to 14 days. **Besifloxacin hydrochloride** (Besivance—Bausch & Lomb) is the sixth fluoroquinolone to be marketed for ophthalmic use for the treatment of bacterial conjunctivitis, joining ciprofloxacin (e.g., Ciloxan), ofloxacin (e.g., Ocuflox), levofloxacin (e.g., Quixin), gatifloxacin (Zymar), and moxifloxacin (Vigamox). However, unlike its predecessors, besifloxacin has not also been marketed in other formulations for the treatment of systemic infections.

Besifloxacin has been demonstrated to be effective against a larger number of specific bacteria than the other fluoroquinolones, although efficacy for the below bacteria (designated with an asterisk) was tested in fewer than 10 infections. Besifloxacin is specifically indicated for the treatment of bacterial conjunctivitis caused by susceptible isolates of the following bacteria: CDC coryneform group G, *Corynebacterium pseudodiphtheriticum*,* *Corynebacterium striatum*,* *Haemophilus influenzae*, *Moraxella lacunata*,* *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Staphylococcus hominis*,* *Staphylococcus lugdunensis*,* *Streptococcus mitis* group, *Streptococcus oralis*, *Streptococcus pneumoniae*, and *Streptococcus salivarius*.* In addition, certain of the other fluoroquinolones have been demonstrated to be effective in the treatment of bacterial conjunctivitis caused by bacteria for which the efficacy of the new drug has not been established (e.g., ofloxacin for infection caused by *Pseudomonas aeruginosa*, moxifloxacin for infection caused by *Chlamydia trachomatis*, levofloxacin and moxifloxacin for infection caused by *Acinetobacter lwoffii*).

The effectiveness of besifloxacin was demonstrated in clinical studies in which the ophthalmic formulation of the drug was compared with its vehicle. Patients treated with the drug experienced a faster rate of resolution of the infection. Clinical resolution of the infection was achieved in 45% of those receiving the drug compared with 33% of those treated with the vehicle. Microbiological outcomes demonstrated eradication rates for the causative pathogens of 91% and 60% in the drug- and vehicle-treated groups, respectively, although microbiologic

eradication does not always correlate with clinical outcomes. Besifloxacin has not been directly compared with other fluoroquinolones in clinical studies.

Ciprofloxacin, levofloxacin, and ofloxacin have also been approved for ophthalmic use in the treatment of corneal ulcers. However, this is not a labeled indication for besifloxacin at the present time.

The use of besifloxacin has been well tolerated, with conjunctival redness (2%) being the ocular adverse event reported most frequently. A risk of superinfection exists with prolonged use. Systemic adverse events are not likely to occur. Patients should not wear contact lenses if they have signs or symptoms of bacterial conjunctivitis or during the course of treatment with the new drug.

Besifloxacin is classified in Pregnancy Category C, but ophthalmic use for a short period of time is not likely to be associated with risk if used in women who are pregnant or nursing. The use of fluoroquinolones for systemic infections is not generally recommended in patients younger than 18 years because of the potential for arthropathies. However, the safety of ophthalmic use of besifloxacin has been demonstrated in children, and it is indicated for use in patients 1 year of age or older.

The recommended dosage of besifloxacin is one drop in the affected eye(s) three times a day (4–12 hours apart) for 7 days. With the exception of moxifloxacin, which has the same dosage regimen, the other ophthalmic fluoroquinolones are administered more frequently, particularly during the first 2 days of treatment, when these agents are usually administered every 2 hours while the patient is awake.

Besifloxacin hydrochloride is supplied as an ophthalmic suspension in an amount equivalent to 6 mg besifloxacin base per mL (0.6%). Benzalkonium chloride is included as a preservative. The bottle should be inverted and shaken once prior to each dose.

The other ophthalmic fluoroquinolones are supplied in solutions, and ciprofloxacin is also available in an ophthalmic ointment.

Pediculicide

For many years, benzyl alcohol has been included as a component of numerous nonprescription combination products that are applied topically and has also been used as an excipient in some solutions that are administered intravenously. However, most recently, it has been evaluated for therapeutic use as a pediculicide, and its approval for this purpose is the basis for its being designated as a “new” drug.

A lotion formulation of **benzyl alcohol** (Ulesfia—Sciele) has been approved for prescription use for the topical treatment of head lice infestation in patients 6 months of age or older. It is thought to inhibit lice from closing their respiratory spiracles, thereby allowing the lotion vehicle to obstruct the spiracles and causing the lice to asphyxiate. This mechanism of action distinguishes benzyl alcohol from other pediculicides such as permethrin (e.g., Nix), pyrethrins with piperonyl butoxide (e.g., RID) that are available without a prescription, and lindane and malathion (Ovide). It has been suggested that the

mechanism of action of benzyl alcohol makes it less vulnerable to the development of resistance, although the previously marketed agents continue to be highly effective.

The effectiveness of benzyl alcohol was demonstrated in two vehicle-controlled studies in which the lotion was applied twice, with an interval of 1 week separating the two applications. In both studies, approximately 75% of patients were free of live lice 14 days after the second treatment. Although benzyl alcohol has not been directly compared with other pediculicides in clinical studies, experience with the other agents has usually been associated with successful treatment in more than 90% of patients.

Pyrethrins with piperonyl butoxide are also approved for treating pubic lice and body lice infestation and lindane for pubic lice infestation. Permethrin and lindane are also approved for treating scabies. However, these are not labeled indications for benzyl alcohol at the present time.

The adverse events most often experienced with the use of benzyl alcohol lotion include pruritus (12%), ocular irritation (6%), application-site irritation (2%), and application-site anesthesia and hypoesthesia (2%). The intravenous use of products containing benzyl alcohol has been associated with neonatal gasping syndrome, with manifestations including gasping respirations, metabolic acidosis, and hypotension. Although the risk of this complication is extremely low with the topical use of benzyl alcohol, its safety has not been demonstrated in patients younger than 6 months, and the product should not be used in children below this age.

Benzyl alcohol is classified in Pregnancy Category B. Whether it is excreted into human milk is unknown, and caution should be exercised if it is used by a nursing woman.

Benzyl alcohol is a liquid that is formulated in a concentration of 5% and supplied as a white topical lotion in 8-oz bottles. The product labeling should be consulted for the guidelines for the amount of lotion to be used per treatment, which are based on the length of the hair. Patients with medium-length hair (4–16 in) may need up to three bottles of lotion, and those with long hair may need up to six bottles. The lotion should be applied to dry hair in a quantity sufficient to completely saturate the scalp and hair. After 10 minutes, the lotion should be completely rinsed off with water. Exposure of the eyes to the lotion should be avoided. If the lotion does come in contact with the eyes, the eyes should be immediately flushed with water.

After the lotion has been washed off the hair, a fine-tooth comb may be used to remove dead lice and nits from the hair and scalp. Although benzyl alcohol kills lice, it is not ovicidal and does not get rid of the lice eggs. Therefore, a second treatment is needed 1 week after the first treatment. In contrast, with the use of permethrin, a single treatment is usually sufficient.

Benzyl alcohol lotion should be used as part of an overall lice management program. All recently worn clothing and hats, as well as bedding and towels, should be washed in hot water or dry cleaned. Personal care items such as combs, brushes, and hair clips should be washed in hot water.

Assessment Questions

Instructions: The assessment test for this activity must be taken online; please see "CPE processing" below for further instructions. There is only one correct answer to each question. This CPE will be available at www.pharmacist.com no later than October 31, 2009.

- Which of the following drug : use pairings is correct?
 - Everolimus : advanced breast cancer
 - Degarelix : prostate cancer
 - Tolvaptan : hypokalemia
 - Benzyl alcohol : scabies
- Which of the following drug : classification pairings is correct?
 - Everolimus : human epidermal growth factor receptor 2 antagonist
 - Degarelix : gonadotropin-releasing hormone receptor agonist
 - Tolvaptan : vasopressin V2 receptor antagonist
 - Plerixafor : mammalian target of rapamycin inhibitor
- Which of the following drug : route of administration pairings is correct?
 - Everolimus : intravenous
 - Degarelix : intramuscular
 - Plerixafor : subcutaneous
 - Besifloxacin : oral
- Which of the following drug : frequency of administration pairings is correct?
 - Tolvaptan : twice a day
 - Benzyl alcohol : twice a day
 - Artemether/lumefantrine : once a day
 - Besifloxacin : three times a day
- With the use of which of the following drugs are hot flashes a common adverse event?
 - Degarelix
 - Plerixafor
 - Tolvaptan
 - Everolimus
- With the use of which of the following drugs is oral ulceration a common adverse event?
 - Artemether/lumefantrine
 - Plerixafor
 - Tolvaptan
 - Everolimus
- Which of the following statements is correct regarding tolvaptan?
 - Its action results in aquaresis.
 - It is administered intravenously in hospitalized patients.
 - It is important that fluids be restricted during the first 24 hours of treatment.
 - Prolongation of the QT interval of the electrocardiogram is the most important concern associated with its use.
- Which of the following statements is correct regarding tolvaptan?
 - Its use must be avoided in patients with impaired renal function.
 - Concurrent use with clarithromycin is contraindicated.
 - Concurrent use with carbamazepine is contraindicated.
 - Concurrent use with cyclosporine is contraindicated.
- Which of the following statements is correct regarding degarelix?
 - It acts by increasing the rate of excretion of testosterone.
 - It must be used concurrently with an antiandrogen such as bicalutamide.
 - It was compared with leuprolide in clinical studies.
 - Serious allergic reactions are the most important risk associated with its use.

CPE Credit:

To obtain 2.0 contact hours of continuing pharmacy education credit (0.2 CEUs) for "New therapeutic agents marketed in the first half of 2009: Part 2," go to 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 October 1, 2012, can receive credit.



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"New therapeutic agents marketed in the first half of 2009: Part 2" is a home-study continuing education activity for pharmacists developed by the American Pharmacists Association.

10. Which of the following statements is correct regarding degarelix?

- a. It is contraindicated in women who are or may become pregnant.
- b. It is extensively metabolized via the cytochrome P450 3A4 metabolic pathway.
- c. Treatment is initiated with a low dose that is titrated to a higher maintenance dosage.
- d. It is administered every 14 days.

11. Which of the following statements is correct regarding everolimus?

- a. It is a prodrug that is converted to its active metabolite sirolimus.
- b. Its antineoplastic activity is attributed to its immunostimulant action.
- c. It is indicated for use after failure of treatment with sunitinib or sorafenib.
- d. It should only be used in a combination regimen with bevacizumab.

12. Which of the following statements is correct regarding everolimus?

- a. Pneumonia is a common adverse event associated with its use.
- b. Increases in blood lipids and glucose occur in many patients and these parameters should be monitored.
- c. It is excreted unchanged in the urine.
- d. It is administered twice a day with food.

13. Which of the following statements is correct regarding plerixafor?

- a. It mobilizes the transfer of hematopoietic stem cells from the bone marrow to the peripheral blood.
- b. It is of the greatest value in treating patients with leukemias.
- c. It acts as a reverse transcriptase inhibitor.
- d. It is administered by adding it to a blood transfusion.

14. Which of the following statements is correct regarding plerixafor?

- a. It is used to permit the use of lower dosages of cytotoxic agents in cancer chemotherapy regimens.
- b. It is used in combination with granulocyte colony-stimulating factor.
- c. It has a slow onset of action, and its full effect is not evident for at least 7 days after initiating treatment.
- d. It is contraindicated in patients with impaired renal function.

15. Which of the following statements is correct regarding artemether/lumefantrine?

- a. Artemether is active against the erythrocytic stage of *Plasmodium falciparum*, and lumefantrine is active against the exoerythrocytic stage.
- b. The two agents are used in combination because they have the same elimination half-lives.
- c. It has been approved for both the treatment and prophylaxis of malaria.
- d. It is effective against strains of *P. falciparum* that are resistant to chloroquine.

16. Which of the following statements is correct regarding artemether/lumefantrine?

- a. It has antifolate activity, and its use should be supplemented with folic acid.
- b. Both agents are excreted in unchanged form in the urine.
- c. It should be administered at least 1 hour before or 2 hours after a meal.
- d. It is used in a 3-day course of therapy in treating malaria.

17. Which of the following statements is correct regarding besifloxacin?

- a. Its spectrum of action includes *Pseudomonas aeruginosa*.
- b. It is available in formulations for oral and ophthalmic use.
- c. It has been demonstrated in comparative studies to be more effective than moxifloxacin.
- d. It is indicated for use in patients 1 year of age or older.

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18. Which of the following statements is correct regarding besifloxacin?

- a. It must be administered more frequently than other fluoroquinolones.
- b. Benzalkonium chloride is included as a preservative in its formulation.
- c. It is more effective than other fluoroquinolones in treating corneal ulcers.
- d. A course of treatment should be continued for 14 days.

19. Which of the following statements is correct regarding benzyl alcohol?

- a. Its spectrum of action includes bacteria, viruses, and parasites.
- b. Its labeled indications include scabies and head lice infestation.
- c. It is thought to act by causing asphyxiation of microorganisms.
- d. It has been demonstrated in comparative studies to be more effective than permethrin.

20. Which of the following statements is correct regarding benzyl alcohol?

- a. It is probably less vulnerable to the development of resistance than most other antimicrobial agents.
- b. It should not be used in children less than 12 years of age.
- c. It is used in two treatments on the same day.
- d. The volume of the formulation used in a treatment should not exceed 8 oz to limit the risk of toxicity.