Abstract

Objective: To provide information regarding the most important properties of the new therapeutic agents marketed in the first half of 2012.

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

Data synthesis: 12 new therapeutic agents were marketed in the United States during the first half of 2012, 6 of which were considered in part 1 of this two-part series. The other 6 agents are considered in this article: peginesatide, axitinib, vismodegib, ingenol mebutate, and glucarpidase. 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.

Conclusion: Vismodegib is the first drug to be approved by FDA for the treatment of metastatic basal cell carcinoma. Pertuzumab inhibits the action of human epidermal growth factor receptor 2 (HER2) and extends progression-free survival when used in combination with trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer who have not received previous anti-HER2 therapy or chemotherapy for metastatic disease. Axitinib is the seventh drug to be approved for the treatment of advanced renal cell carcinoma since 2005 and is indicated for use in patients who have failed one previous systemic therapy. Ingenol mebutate is indicated for the topical treatment of actinic keratosis. Like its predecessors that are administered topically, it causes dermatologic adverse events in most patients. However, the effectiveness of ingenol mebutate in a 2- or 3-day course of treatment is an important advantage over the other drugs with which treatment is often continued for weeks or months. Glucarpidase rapidly converts methotrexate to inactive metabolites and is indicated for the treatment of toxic plasma methotrexate concentrations in patients with delayed methotrexate clearance resulting from impaired renal function. Peginesatide is an erythropoiesis-stimulating agent with properties that are similar to those of epoetin alfa and darbepoetin alfa. However, it has a longer duration of action and is administered once a month for the treatment of anemia due to chronic kidney disease in adult patients on dialysis.

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

www.pharmacist.com
Erythropoiesis-stimulating agent

Chronic kidney disease (CKD) is associated with a progressive decline in renal function that may eventually result in a need for dialysis or renal transplantation. More than 400,000 people in the United States are on dialysis. One of the complications of CKD is that the kidneys produce less erythropoietin, the hormone that stimulates red blood cell production. The reduction in the formation of red blood cells results in anemia, and almost all patients with CKD of a severity that requires dialysis experience anemia to a degree that necessitates treatment.

Erythropoiesis-stimulating agents (ESAs) are the standard of treatment for anemia caused by CKD. They stimulate the bone marrow to produce more red blood cells, usually measured as hemoglobin (Hb) concentrations, and reduce or avoid the need for transfusions. Epoetin alfa (Epogen, Procrit) was the first ESA and is usually administered three times a week. Darbepoetin alfa (Aranesp) has a longer duration of action and is administered once a week or once every 2 weeks. Both agents are produced using recombinant DNA technology. Epoetin alfa contains the identical amino acid sequence of natural erythropoietin, and darbepoetin alfa is a modified form of erythropoietin.

Peginesatide acetate (Omontys—Affymax; Takeda) is the third ESA to be marketed in the United States, and is a synthetic, pegylated dimeric peptide, the amino acid components of which are arranged in a different order than those in erythropoietin. Like epoetin alfa and darbepoetin alfa, it is administered subcutaneously or intravenously. Peginesatide is indicated for the treatment of anemia due to chronic kidney disease in adult patients on dialysis. It was evaluated in two studies in patients with Hb concentrations initially stabilized with the use of epoetin alfa treatment who either continued their current treatment or received peginesatide once a month. The new drug was demonstrated to be as effective and safe as epoetin alfa in maintaining Hb concentrations within the prespecified range of 10 to 12 g/dL.

The labeled indication for peginesatide is more limited than the indications for epoetin alfa and darbepoetin alfa. The latter two agents are also indicated for the treatment of anemia caused by CKD in patients not on dialysis, as well as in children and adults, and for the treatment of anemia in patients with nonmyeloid malignancies in whom anemia results from the effect of concomitant myelosuppressive chemotherapy. In addition, epoetin alfa is indicated for the treatment of anemia caused by zidovudine in human immunodeficiency virus–infected patients and for the reduction of allogeneic RBC transfusions in patients undergoing elective noncardiac, nonvascular surgery.

The labeling for the three ESAs also includes a section on the limitations of use for the drugs. For peginesatide, it is noted that the drug is not recommended for use in patients with CKD who are not on dialysis, in patients requiring treatment for cancer and whose anemia is not caused by CKD, or as a substitute for red blood cell transfusions in patients who require immediate correction of anemia. Peginesatide also has not been shown to improve symptoms, physical functioning, or health-related quality of life.

The labeling for the ESAs also includes a boxed warning identifying an increased risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence. The warning further notes that patients experienced greater risks for death, serious cardiovascular reactions, and stroke when administered ESAs to target an Hb concentration greater than 11 g/dL; that no trial has identified an Hb target concentration, ESA dose, or dosing strategy that does not increase these risks; and that the ESA should be used in the lowest dosage needed to reduce the need for red blood cell transfusions. The boxed warnings are more extensive in the labeling for epoetin alfa and darbepoetin alfa, noting the serious risks associated with their use for the additional indications for which they are approved.

Peginesatide is contraindicated in patients with uncontrolled hypertension. Hypertension should be appropriately controlled before initiation of and during treatment with peginesatide. The drug should be reduced or withheld if blood pressure becomes difficult to control. Following initiation of treatment with peginesatide, patients may require adjustment of their dialysis prescription. Increased anticoagulation with heparin may also be needed to prevent clotting of the extracorporeal circuit during hemodialysis.

Most patients with CKD will require supplemental iron during the course of ESA therapy. Transferrin saturation and serum ferritin should be evaluated before and during peginesatide treatment. Supplemental iron therapy should be provided when serum ferritin is less than 100 μg/L or when

---

**Preassessment questions**

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

1. Which of the following agents is indicated for use in combination with trastuzumab and docetaxel?
   a. Peginesatide
   b. Pertuzumab
   c. Axitinib
   d. Glucarpidase

2. With the use of which of the following agents is hypertension a common adverse event?
   a. Axitinib
   b. Glucarpidase
   c. Vismodegib
   d. Pertuzumab

3. Which of the following statements is correct regarding peginesatide?
   a. It is a prodrug that is converted to epoetin alfa following administration.
   b. It contains the same sequence of amino acid components as naturally-occurring erythropoietin.
   c. It stimulates the bone marrow to produce more white blood cells.
   d. It is indicated for the treatment of anemia due to chronic kidney disease in adult patients on dialysis.
serum transferrin saturation is less than 20%.

The type and incidence of adverse events experienced by patients treated with peginesatide are similar to those reported in patients treated with epoetin alfa. The adverse events that occurred most often in the clinical studies of peginesatide included diarrhea (18%), dyspnea (18%), nausea (17%), cough (16%), and arteriovenous fistula site complication (16%). With the use of epoetin alfa and darbepoetin alfa, there have been reports of pure red cell aplasia and of severe anemia that arise following the development of neutralizing antibodies to erythropoietin. Only approximately 1% of the patients treated with peginesatide had detectable concentrations of peginesatide-specific binding antibodies, and there were no reports of pure red cell aplasia in the clinical studies.

Peginesatide is classified in Pregnancy Category C and should only be used during pregnancy if the anticipated benefit justifies the risk to the fetus. The effectiveness and safety of the new drug in pediatric patients have not been established.

Peginesatide is administered as a subcutaneous or intravenous injection once a month, and the opportunity to administer it less frequently than the other ESAs is an important advantage. Subcutaneous injections may be administered in the outer area of the upper arms, the front of the middle thighs, the abdomen (except for the 2-inch area around the navel), or the upper outer area of the buttocks. Intravenous doses are given in the access port on the dialysis tubing while dialysis is under way. The product labeling includes detailed instructions for use that should be provided to patients or caregivers who have been trained to administer peginesatide at home.

Treatment should be initiated when the Hb concentration is less than 10 g/dL. The recommended initial dosage in patients who are not currently treated with an ESA is 0.04 mg/kg once a month. For patients previously receiving epoetin alfa or darbepoetin alfa, the starting monthly dose of peginesatide should be estimated on the basis of the weekly dose of the previous agent at the time of substitution, using the guidelines included in the product labeling. For patients previously treated with epoetin alfa, the first dose of peginesatide should be administered 1 week after the last epoetin alfa dose was administered. For patients previously treated with darbepoetin alfa, the first dose of peginesatide should be administered at the next scheduled dose in place of darbepoetin alfa.

Hb concentrations should be monitored at least every 2 weeks until stable, then at least monthly. If the Hb rises rapidly (e.g., more than 1 g/dL in the 2 weeks before the dose or more than 2 g/dL in 4 weeks), the dosage of peginesatide should be reduced by 25% or more as needed to reduce rapid responses. If the Hb approaches or exceeds 11 g/dL, the dosage should be reduced or treatment interrupted. After a dose has been withheld and once the Hb begins to decrease, peginesatide may be restarted at a dose approximately 25% below the previously administered dose. For patients who do not respond adequately, if the Hb has not increased by more than 1 g/dL after 4 weeks of therapy, the dosage should be increased by 25%.

Peginesatide injection is supplied as a solution in single-use vials containing 2, 3, 4, 5, and 6 mg (each dose in a volume of 0.5 mL); single-use prefilled syringes containing 1, 2, 3, 4, 5, and 6 mg (each dose in a volume of 0.5 mL); and multiple-use vials (10 mg/mL and 20 mg/2 mL). The products should be stored in a refrigerator.

Antineoplastic drugs

Axitinib
Renal cell carcinoma is the most common type of kidney cancer. Early detection and surgery may result in a cure for some patients, but in an estimated 25% of patients, the disease is already advanced at the time of initial diagnosis. Before 2005, the treatment options for advanced renal cell carcinoma were very limited. However, since then, seven drugs have been approved for this indication. Axitinib (Inlyta—Pfizer) is the newest of these agents and joins sorafenib (Nexavar), sunitinib (Sutent), pazopanib (Votrient), temsirolimus (Torisel), everolimus (Afinitor), and bevacizumab (Avastin), with the latter agent having been initially approved for the treatment of colorectal cancer and subsequently for additional indications including renal cell carcinoma, for which

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Therapeutic classification</th>
<th>Route of administration</th>
<th>FDA classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib</td>
<td>Inlyta</td>
<td>Pfizer</td>
<td>Antineoplastic agent</td>
<td>Oral</td>
<td>1-S</td>
</tr>
<tr>
<td>Glucarpidase</td>
<td>Voraxaze</td>
<td>BTG</td>
<td>Antidote</td>
<td>Intravenous</td>
<td>P-</td>
</tr>
<tr>
<td>Ingenol mebutate</td>
<td>Picato</td>
<td>LEO</td>
<td>Agent for actinic keratosis</td>
<td>Topical</td>
<td>1-S</td>
</tr>
<tr>
<td>Peginesatide acetate</td>
<td>Omontys</td>
<td>Affymax; Takeda</td>
<td>Erythropoiesis-stimulating agent</td>
<td>Intravenous; subcutaneous</td>
<td>1-S</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Perjeta</td>
<td>Genentech</td>
<td>Antineoplastic agent</td>
<td>Intravenous</td>
<td>P-</td>
</tr>
<tr>
<td>Vismodegib</td>
<td>Erivedge</td>
<td>Genentech</td>
<td>Antineoplastic agent</td>
<td>Oral</td>
<td>1-P</td>
</tr>
</tbody>
</table>

*Additional agents marketed in this time period are considered in part 1 of this two-part series (Pharmacy Today. 2012[Sep];19[9]:86–96).

*FDA classification of new drugs: 1 = new molecular entity; P = priority review; S = standard review.

*A biological approved through an FDA procedure that does not assign a numerical classification.
it is used in combination with interferon alfa.

Certain kinases, including multiple vascular endothelial growth factor (VEGF) receptors, have been associated with tumor growth and progression of renal cell carcinoma. Axitinib is a kinase inhibitor and has been demonstrated to inhibit receptor tyrosine kinases, including VEGF receptors 1, 2, and 3. The new drug is specifically indicated for the treatment of advanced renal cell carcinoma after failure of one previous systemic therapy.

The effectiveness of axitinib was demonstrated in a study in which axitinib or sorafenib was used in treating patients whose disease had progressed on or after treatment with one previous systemic therapy (other than sorafenib). Progression-free survival was the primary endpoint in the study, and the patients treated with axitinib had a median progression-free survival of 6.7 months compared with 4.7 months in patients treated with sorafenib.

Axitinib is also being evaluated for the treatment of other cancers such as non–small-cell lung cancer, melanoma, prostate cancer, and advanced pancreatic cancer. However, these are not labeled indications currently.

The use of axitinib has been associated with the occurrence of numerous adverse events. Hypertension was reported in 40% of patients treated with the drug in the clinical study, and blood pressure should be well controlled before initiating treatment. Patients should be monitored for hypertension and treated with antihypertensive agents as needed. Arterial (e.g., myocardial infarction, transient ischemic attacks) and venous (e.g., deep-vein thrombosis, pulmonary embolism) thromboembolic events of grade 3 or 4 severity have been reported in 1% and 3% of patients, respectively, and particular caution must be exercised in patients who are at increased risk of these occurrences. Hemorrhagic events were experienced by 16% of patients, and the drug should not be used in patients with evidence of untreated brain metastasis or recent active gastrointestinal bleeding. Treatment with axitinib should be stopped at least 24 hours before scheduled surgery.

Gastrointestinal perforation and fistula formation were each experienced by 1% of patients treated with axitinib, and patients should be monitored for symptoms of these complications periodically throughout treatment. There have been rare reports of reversible posterior leukoencephalopathy syndrome in patients treated with the new agent, and treatment should be permanently discontinued if this problem is experienced.

Hypothyroidism was reported in 19% of patients in the controlled clinical study, and thyroid function should be monitored before initiation of and periodically throughout treatment. Thyroid hormone replacement therapy should be initiated, as needed. Proteinuria (11%) and elevations of alanine aminotransferase (22%) have been experienced, and monitoring of these parameters should be done before initiation of and periodically throughout treatment.

In addition to hypertension (40%), the most frequently experienced adverse events with the use of axitinib included diarrhea (55%), fatigue (39%), decreased appetite (34%), nausea (32%), dysphonia (31%), palmar–plantar erythrodysesthesia (hand–foot) syndrome (27%), decreased weight (25%), vomiting (24%), asthenia (21%), and constipation (20%).

Axitinib may cause fetal harm if administered to a pregnant woman and is classified in Pregnancy Category D. Women of childbearing potential should be warned to avoid becoming pregnant while being treated with the drug. Although whether the drug 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 axitinib in pediatric patients have not been established.

Following oral administration, the mean absolute bioavailability of axitinib is 58%. The drug may be administered without regard to food and is metabolized primarily in the liver via the cytochrome P450 (CYP)3A4/5 pathways. Approximately 41% of a dose is recovered in the feces and approximately 23% in the urine. In patients with mild hepatic impairment, an adjustment of the initial dosage is not necessary, but a reduction in the initial dosage is recommended in patients with moderate hepatic impairment. Axitinib has not been studied in patients with severe hepatic impairment. An adjustment in dosage is not necessary in patients with impaired renal function.

The exposure and activity of axitinib is increased by ketoconazole, and the concurrent use of this agent or another strong CYP3A4/5 inhibitor, as well as grapefruit products, should be avoided. If a strong CYP3A4/5 inhibitor must be used concomitantly, the dosage of axitinib should be reduced. Strong inducers of CYP3A4/5 (e.g., rifampin, carbamazepine, dexamethasone, St. John’s wort) would be expected to reduce the exposure and activity of axitinib, and concurrent use should be avoided.

The recommended initial dosage of axitinib is 5 mg twice a day, with administration of the doses approximately 12 hours apart. Tablets are supplied in 1 and 5 mg potencies and should be swallowed whole with a glass of water. If the patient vomits or misses a dose, an additional dose should not be taken and the next prescribed dose should be taken at the usual time.

Adjustments in dosage may be made based on safety and tolerability considerations. For patients who tolerate axitinib for at least 2 consecutive weeks with no adverse events occurring at greater than a grade 2 severity, are normotensive, and are not receiving antihypertensive medication, the dosage may be increased. The dosage may be increased from 5 mg twice a day to 7 mg twice a day and subsequently to 10 mg twice a day using the same criteria.

Some patients may experience adverse events that may require a reduction in dosage. If dose reduction from 5 mg twice a day is necessary, the recommended dosage is 3 mg twice a day. If additional dose reduction is required, the recommended dosage is 2 mg twice a day.

If using a strong CYP3A4/5 inhibitor is necessary in a patient being treated with axitinib, the dosage of the new drug should be reduced by approximately one-half. A similar reduction in dosage is recommended in patients with moderate hepatic impairment.
Pertuzumab

Breast cancer is the second most frequent cause of cancer-related death among women, and an estimated 40,000 women will die from the disease in 2012. Human epidermal growth factor receptor 2 (HER2) is a protein involved in normal cell growth but is overexpressed in approximately 20% of breast cancers. Increased amounts of this protein (i.e., HER2 positive) contribute to the growth and survival of cancer cells and are often associated with more aggressive disease. The humanized monoclonal antibody, trastuzumab (Herceptin) was marketed in 1998 as the first anti-HER2 treatment and is used as a first-line treatment for patients with HER2-positive metastatic breast cancer. Its antitumor activity is attributed to binding to subdomain IV of the HER2 extracellular domain.

Pertuzumab (Perjeta—Genentech) is also an anti-HER2 humanized monoclonal antibody, but it targets a different domain than trastuzumab. The new drug targets the extracellular dimerization domain (subdomain II) of the HER2 protein and blocks ligand-dependent heterodimerization of HER2 with other HER family members. This results in inhibition of intracellular signaling through two major signal pathways, resulting in cell growth arrest and apoptosis. Although pertuzumab alone inhibits the growth of tumor cells, its inhibition of a different function of the HER2 protein complements the action of trastuzumab and its use with the latter agent provides an augmented antitumor effect.

Pertuzumab is administered intravenously and is indicated for use in combination with trastuzumab and docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received previous anti-HER2 therapy or chemotherapy for metastatic disease. The detection of HER2 overexpression is necessary for the selection of patients who are appropriate for therapy. The effectiveness of pertuzumab was demonstrated in a clinical trial in which patients received either the new drug plus trastuzumab and docetaxel or placebo plus trastuzumab and docetaxel. The primary endpoint was progression-free survival. The median progression-free survival in the patients treated with the pertuzumab regimen was 18.5 months, which was significantly longer than the median progression-free survival of 12.4 months in patients who received placebo plus trastuzumab and docetaxel.

Pertuzumab is also being studied in patients with other types of cancer, including gastric carcinoma, colorectal cancer, and castration-resistant prostate cancer. However, these are not labeled indications at the present time.

Embryo–fetal death and birth defects are possible if pertuzumab is used during pregnancy, and this is the subject of a boxed warning in its labeling. The drug is classified in Pregnancy Category D, and pregnancy status should be verified before initiating treatment. Women of reproductive potential should be advised to use effective contraception while being treated with the drug and for 6 months following the last dose.

Decreases in left ventricular ejection fraction (LVEF) have been reported with drugs that inhibit HER2 activity, but in the clinical trial, the use of pertuzumab was not associated with decreases in LVEF or increases in the incidence of symptomatic left ventricular systolic dysfunction compared with placebo plus trastuzumab and docetaxel. Pertuzumab has not been studied in patients with impaired left ventricular function or conditions that could increase the risk of it. LVEF should be assessed before initiating treatment and at regular intervals (e.g., every 3 months) during treatment.

Some patients have experienced infusion and hypersensitivity reactions following administration of pertuzumab, with the most common events including pyrexia, chills, fatigue, headache, asthenia, hypersensitivity, and vomiting. The overall frequency of hypersensitivity/anaphylaxis reactions was 11% in patients treated with the pertuzumab regimen and 9% in the placebo-treated group, with approximately 2% of the reactions being grades 3 to 4 in severity. Patients should be closely observed for 60 minutes after the first infusion and for 30 minutes after subsequent infusions.

The most frequently experienced adverse events in the clinical trial with the pertuzumab regimen included diarrhea (67%), alopecia (61%), neutropenia (53%), nausea (42%), fatigue (38%), rash (34%), and peripheral neuropathy (32%). The incidence of diarrhea and rash was significantly higher in patients treated with the new drug, whereas the incidence of the other above-mentioned events was similar to that observed in the patients receiving placebo plus trastuzumab and docetaxel. In both groups of patients, neutropenia was almost always of a grade 3 to 4 severity, but the incidence of febrile neutropenia was higher in patients treated with pertuzumab (14%) than in those receiving placebo (8%). An increased incidence of febrile neutropenia was observed for Asian patients in both treatment arms.

Although whether pertuzumab 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 the new drug in pediatric patients have not been established.

Pertuzumab is administered by intravenous infusion and must not be administered as an intravenous push or bolus. Patients should be closely observed during and following administration of the drug because of the risk of infusion/hypersensitivity reactions. The initial dose of pertuzumab is 840 mg administered as a 60-minute intravenous infusion, followed every 3 weeks thereafter by a dose of 420 mg administered over 30 to 60 minutes. The infusion rate may be slowed or interrupted if the patient experiences an infusion-associated reaction. If a serious hypersensitivity reaction occurs, the infusion should be discontinued immediately.

When administered with pertuzumab, the recommended initial dose of trastuzumab is 8 mg/kg administered as a 90-minute intravenous infusion, followed every 3 weeks thereafter by a dose of 6 mg/kg administered over 30 to 90 minutes. When administered with pertuzumab, the recommended dose of docetaxel is 75 mg/m² administered as an intravenous infusion. The dose may be increased to 100 mg/
m² administered every 3 weeks if the initial dose is well tolerated.

The use of pertuzumab and trastuzumab should be withheld for at least 3 weeks if there is a drop in LVEF to less than 40% or if there is an LVEF of 40% to 45% with a 10% or greater absolute decrease below pretreatment values. Pertuzumab should be withheld or discontinued if trastuzumab treatment is withheld or discontinued. If docetaxel is discontinued, treatment with pertuzumab and trastuzumab may be continued.

Pertuzumab is supplied in single-use vials containing 420 mg of the drug in a solution with a drug concentration of 30 mg/mL. The vials should be stored in a refrigerator. When preparing the solution for infusion, the appropriate volume of pertuzumab solution should be withdrawn from the vial and diluted into a 250 mL 0.9% Sodium Chloride Injection PVC or non-PVC polyolefin infusion bag. The diluted solution should be mixed by gentle inversion but should not be shaken. After it is prepared, the infusion of the solution should be initiated immediately. If the diluted solution cannot be used immediately, it may be stored in a refrigerator for up to 24 hours. Only Sodium Chloride Injection should be used in diluting pertuzumab, and Dextrose (5%) solution must not be used.

Vismodegib
Basal cell carcinoma is the most common type of skin cancer and develops on areas of skin that are regularly exposed to sunlight or other ultraviolet radiation. It starts in the epidermis and is usually a slow-growing, painless form of skin cancer. The treatment of basal cell carcinoma has included excision, radiation therapy, cryosurgery, laser beam light exposure, and topical therapies (e.g., imiquimod). Surgical procedures usually result in a high cure rate, but some patients are not candidates for surgery and some who have had surgery experience recurrence of the cancer. The use of systemic therapies (e.g., cisplatin) has been of limited benefit.

Most basal cell cancers are associated with excessive activity of a molecular pathway designated as the Hedgehog pathway. This pathway is primarily active during embryologic development, but following fetal development, this pathway is essentially inactive in most individuals. However, if reactivation occurs, such as is experienced by many patients with basal cell carcinoma, stimulation of cell growth and proliferation occurs.

Vismodegib (Erivedge—Genentech) is an inhibitor of the Hedgehog pathway and acts by binding to and inhibiting Smoothened, a transmembrane protein involved in Hedgehog signal transduction. It is indicated for the treatment of adults with metastatic basal cell carcinoma or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery and who are not candidates for radiation. It is the first drug to be approved by FDA for the treatment of metastatic basal cell carcinoma.

The effectiveness of vismodegib was demonstrated in a multicenter study in 96 patients. The primary endpoint of the study was the objective response rate (i.e., the percentage of patients who experienced complete or partial shrinkage or disappearance of the cancerous lesions). Of the patients with metastatic disease, 30% experienced a partial response, and 43% of those with locally advanced disease experienced a complete (21%) or partial (22%) response. The median response duration in both groups of patients was 7.6 months.

The most important concern with the use of vismodegib is the risk of embryo–fetal death or severe birth defects if the drug is used during pregnancy. This is the subject of a boxed warning in the labeling for vismodegib, and it is classified in Pregnancy Category D. In female patients of reproductive potential, pregnancy status should be determined within 7 days before initiating treatment. Those with a negative pregnancy test should use a highly effective form of contraception during therapy and for 7 months following the last dose of vismodegib. Male patients should use condoms with spermicide, even after a vasectomy, during sexual intercourse while being treated with the drug and for 2 months after the last dose to avoid exposing an embryo or fetus to the drug. Women who may have been exposed to vismodegib during pregnancy, either directly or through seminal fluid, should be encouraged to participate in the Erivedge pregnancy pharmacovigilance program by calling 888-835-2555. Patients treated with vismodegib should not donate blood or blood products during the period of treatment and for 7 months following the last dose.

The adverse events experienced most frequently in the clinical study of vismodegib included muscle spasms (72%), alopecia (64%), dysgeusia (alteration of taste; 55%), weight loss (45%), fatigue (40%), nausea (30%), diarrhea (29%), decreased appetite (25%), constipation (21%), arthralgias (16%), vomiting (14%), and ageusia (loss of taste; 11%). Whether vismodegib is excreted in human milk is not known, but a decision should be made to discontinue nursing or not use the drug. The effectiveness and safety of the new drug in pediatric patients have not been established.

Vismodegib is administered orally and may be taken without regard to meals. The absolute bioavailability is approximately 32% following a single dose. Metabolism is limited, and the parent drug is the predominant form in the circulation. It is primarily eliminated as unchanged drug, and more than 80% of a dose is recovered in the feces. The effects of hepatic and renal impairment on the exposure and activity of vismodegib have not been studied but are not expected to be of clinical importance.

Medications that increase the pH of the upper gastrointestinal tract (proton pump inhibitors, histamine H₂ receptor antagonists, antacids) may alter the solubility of vismodegib and reduce its bioavailability. This potential interaction has not been evaluated in formal studies, but the concurrent use of these agents that reduce gastric acidity is best avoided.

The recommended dosage of vismodegib is 150 mg once a day until the disease worsens or unacceptable toxicity is experienced. If a dose is missed, it should not be taken at a
later time and treatment should be resumed with the next scheduled dose.

Vismodegib capsules are supplied in a 150-mg potency. The capsules should be swallowed whole and should not be opened or crushed.

Agent for actinic keratosis

Actinic keratosis is a dry, scaly, rough-textured patch or lesion that forms on the outermost layer of the skin following cumulative exposure to ultraviolet light, such as sunlight. Often called sun spots and/or age spots, the lesions may be pink, red, gray, or the same color as the skin and may be easier to feel than see. A job or other activities involving many hours spent outside can result in skin damage if the skin isn’t adequately protected. Individuals at risk for actinic keratoses are often fair-skinned men and women older than 40 years who have accumulated a considerable amount of sun exposure over a period of many years.

Approximately one in five Americans develop skin cancer. Actinic keratoses are experienced by almost 60 million Americans and are the most common precancerous condition. They have the potential to progress to squamous cell carcinoma, a type of nonmelanoma skin cancer that is the second most common type of skin cancer. An estimated 65% of squamous cell carcinomas begin as untreated actinic keratoses. The risk of squamous cell carcinoma increases with the number of lesions present, and predicting which lesions will develop into skin cancer is not possible.

The treatment of actinic keratoses has included cryosurgery, photodynamic therapy, and the topical application of medications such as fluorouracil (e.g., Carac), imiquimod (e.g., Aldara), and diclofenac (e.g., Solaraze). However, treatment with these agents must be continued for weeks to months, and local adverse events are frequently experienced with their use.

Ingenol mebutate gel is applied to the affected area, up to one contiguous skin area of approximately 25 cm². After opening or crushed.

Application site pain and pruritus were experienced by some patients, more commonly in those with lesions on the face and scalp, in whom the frequency of pain and pruritus were 15% and 8%, respectively. Because of the risk of severe eye disorders (e.g., pain, eyelid edema, periorbital edema), caution must be observed in avoiding contact of the drug with the periocular area. Patients should wash their hands immediately after applying the medication and avoid transferring the drug to other areas, including the eyes. If accidental exposure of the eyes occurs, the area should be flushed with water and medical care should be sought as soon as possible.

Ingenol mebutate 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 patients younger than 18 years of age.

Ingenol mebutate gel is supplied in two concentrations, 0.015% and 0.05%, in unit–dose tubes. The product should be stored in a refrigerator. For the treatment of actinic keratoses on the face and scalp, the 0.015% gel should be applied to the affected area once a day for 2 consecutive days. The duration of topical treatment for actinic keratoses with fluorouracil, imiquimod, and diclofenac is continued for weeks to months. Like ingenol mebutate, the use of these agents is often associated with the occurrence of dermatologic adverse events and this is a reason for which some patients are nonadherent with longer treatment regimens. The shorter treatment regimen for ingenol mebutate is an important advantage for the new drug. In addition to the greater convenience of administration, patients are more likely to be adherent in completing the 2- or 3-day course of treatment.

Ingenol mebutate gel is applied to the affected area, up to one contiguous skin area of approximately 25 cm². After
spreading evenly over the treatment area, the gel should be allowed to dry for 15 minutes. Patients should avoid washing and touching the treated area for a period of 6 hours after application. Following this time, patients may wash the area with a mild soap.

Antidote
Methotrexate is used in high doses in the treatment of certain malignancies, including leukemias, lymphomas, and osteosarcoma. The use of high doses increases the risk of adverse events associated with the drug such as nephrotoxicity (e.g., kidney failure), hepatotoxicity, bone marrow suppression, oral and gastrointestinal ulceration, and dermatologic reactions. Methotrexate is eliminated primarily via the kidneys and the impairment of renal function, whether preexisting or developing as a consequence of treatment, results in delayed excretion, higher serum concentrations, and an increased risk of adverse events. Although leucovorin is used to diminish cytotoxicity resulting from the use of high doses of methotrexate, it is of limited benefit in patients who can’t adequately eliminate the drug.

Glucarpidase (Voraxaze—BTG) is a carboxypeptidase enzyme produced by recombinant DNA technology. It rapidly converts methotrexate to its inactive metabolites glutamate and 4-deoxy-4-amino-N10-methylpteroyl acid (DAMPA). These metabolites are eliminated primarily via the liver, and the new drug provides an alternate nonrenal pathway for methotrexate elimination. Glucarpidase is administered as a single intravenous injection and is indicated for the treatment of toxic plasma methotrexate concentrations (>1 μmol/L) in patients with delayed methotrexate clearance resulting from impaired renal function.

The effectiveness of glucarpidase was demonstrated in a study in 22 patients in which the treatment was considered successful if the methotrexate concentration fell below a critical concentration within 15 minutes and stayed below this concentration for 8 days. Ten patients achieved this goal, and all patients eliminated 95% of the methotrexate.

Glucarpidase is not indicated for use in patients who exhibit the expected clearance of methotrexate or those with normal or mildly impaired renal function because of the potential risk of subtherapeutic exposure to methotrexate.

The folate derivative leucovorin often is used with high-dose methotrexate treatment to reduce the risk of certain toxicities (i.e., leucovorin rescue). Leucovorin should continue to be used after the administration of glucarpidase but, because it is a substrate for the new drug, it should not be administered within 2 hours before or after a dose of glucarpidase. For the first 48 hours following the administration of glucarpidase, the same dosage of leucovorin should be used as was given before administration of glucarpidase. Beyond 48 hours after the administration of glucarpidase, the dosage of leucovorin should be based on the measured methotrexate concentration. Treatment with leucovorin should be continued until the methotrexate concentration has been maintained below the leucovorin treatment threshold for a minimum of 3 days. Hydration and alkalinization of the urine should be continued as indicated.

The inactive DAMPA metabolite of methotrexate that is formed following the administration of glucarpidase interferes with the measurement of methotrexate concentrations using immunoassays, and these assays are not reliable for samples collected within 48 hours following the administration of glucarpidase. Methotrexate concentrations within 48 hours following administration of glucarpidase can only be reliably measured by a chromatographic method.

The safety of glucarpidase was assessed using data from 290 patients. Serious allergic reactions were experienced infrequently (in <1% of patients). The most commonly reported adverse events included paresthesias (2%), flushing (2%), nausea/vomiting (2%), headache (1%), and hypotension (1%). Anti-glucarpidase antibodies were identified in 17% of patients.

Glucarpidase is classified in Pregnancy Category C. Whether it is excreted in breast milk is not known, and caution should be exercised if it is administered to a nursing woman. Of the 22 patients in the study in whom the efficacy of glucarpidase was evaluated, 12 were pediatric patients with ages ranging from 5 to 16 years.

The recommended dosage of glucarpidase is a single dose of 50 units/kg. The drug is administered as a bolus intravenous injection over 5 minutes.

Glucarpidase is supplied in a lyophilized powder in single-use vials containing 1,000 units of the drug. The vials should be stored in a refrigerator. The contents of the vial should be reconstituted with 1 mL sterile saline for injection. The vial should be rolled and tilted gently to mix the contents but should not be shaken. The reconstituted solution should be used immediately or stored under refrigeration for up to 4 hours if not used immediately.
CPE assessment

Instructions: This exam must be taken online; please see “CPE information” for further instructions. The online system will present these questions in random order to help reinforce the learning opportunity. There is only one correct answer to each question.

1. Which of the following agents is administered orally?
   a. Ingenol mebutate
   b. Glucarpidase
   c. Vismodegib
   d. Peginesatide

2. Which of the following agents is indicated for use in combination with trastuzumab and docetaxel?
   a. Peginesatide
   b. Pertuzumab
   c. Axitinib
   d. Glucarpidase

3. Which of the following agents is used in a 2- or 3-day course of treatment?
   a. Vismodegib
   b. Axitinib
   c. Pertuzumab
   d. Ingenol mebutate

4. With the use of which of the following agents is hypertension a common adverse event?
   a. Axitinib
   b. Glucarpidase
   c. Vismodegib
   d. Pertuzumab

5. Patients treated with which of the following agents are most likely to require supplemental iron?
   a. Pertuzumab
   b. Peginesatide
   c. Axitinib
   d. Ingenol mebutate

6. Patients treated with which of the following agents should not donate blood or blood products during the period of treatment and for 7 months following the last dose?
   a. Peginesatide
   b. Axitinib
   c. Ingenol mebutate
   d. Vismodegib

7. Which of the following statements is correct regarding peginesatide?
   a. It is a prodrug that is converted to epoetin alfa following administration.
   b. It contains the same sequence of amino acid components as naturally occurring erythropoietin.
   c. It stimulates the bone marrow to produce more white blood cells.
   d. It is indicated for the treatment of anemia resulting from chronic kidney disease in adult patients on dialysis.

8. Which of the following statements is correct regarding peginesatide?
   a. The goal of treatment is to increase hemoglobin concentrations above 14 g/dL.
   b. It is more likely than epoetin alfa to cause pure red cell aplasia.
   c. It is administered once a month.
   d. It is administered intramuscularly.

9. Which of the following statements is correct regarding peginesatide?
   a. It is less effective than epoetin alfa.
   b. It is more likely than epoetin alfa to be associated with the development of neutralizing antibodies.
   c. Blood pressure should be monitored and appropriately controlled during treatment.
   d. Constipation is the adverse event most often associated with its use.

10. Which of the following statements is correct regarding axitinib?
    a. It is classified as a kinase inhibitor.
    b. It has been approved for first-line use for the treatment of advanced renal cell carcinoma.
    c. It should be used as part of a combination regimen with sorafenib.
    d. It has been demonstrated to be more effective than everolimus in extending progression-free survival.

11. Which of the following statements is correct regarding axitinib?
    a. Hyperthyroidism is commonly associated with its use.
    b. Hemorrhagic events may occur and treatment should be stopped at least 24 hours before scheduled surgery.
    c. Alopecia is one of the most common adverse events with its use.
    d. It should be administered with a high-fat meal.

12. Which of the following statements is correct regarding axitinib?
    a. It is administered once a day.
    b. It is eliminated in unchanged form via the kidneys.
    c. Its dosage should be reduced in patients with moderate or severe renal impairment.
    d. Its dosage should be reduced in patients who are also being treated with a strong cytochrome P450 (CYP)3A4/5 inhibitor.
13. Which of the following statements is correct regarding pertuzumab?
   a. It is the active metabolite of trastuzumab.
   b. It acts by inhibiting a function of the human epidermal growth factor receptor 2 protein.
   c. It is indicated for the treatment of metastatic breast cancer in patients who have not experienced an adequate response with trastuzumab.
   d. It is classified as a kinase inhibitor.

14. Which of the following statements is correct regarding pertuzumab?
   a. It is associated with a risk of embryo–fetal death and birth defects if used during pregnancy.
   b. It is administered by intravenous injection over a period of 5 minutes.
   c. It is administered once a week.
   d. It is metabolized primarily via the CYP3A4 metabolic pathway.

15. Which of the following statements is correct regarding vismodegib?
   a. It is classified as a monoclonal antibody.
   b. It is classified as a kinase inhibitor.
   c. It acts as an inhibitor of the Hedgehog pathway.
   d. Its labeled indications include the treatment of squamous cell carcinoma.

16. Which of the following statements is correct regarding vismodegib?
   a. It is the first drug to be approved by FDA for the treatment of metastatic basal cell carcinoma.
   b. It should be administered with a high-fat meal.
   c. It is extensively metabolized via the CYP2D6 pathway.
   d. The concurrent use of omeprazole may increase its bioavailability and activity.

17. Which of the following statements is correct regarding vismodegib?
   a. It prolongs the QT interval of the electrocardiogram and should not be used concurrently with other medications having this same action.
   b. It may cause hepatotoxicity, and liver function tests should be monitored during its use.
   c. It may cause hypothyroidism, and thyroid function should be monitored during its use.
   d. It is associated with a risk of embryo–fetal death and birth defects if used during pregnancy.

18. Which of the following statements is correct regarding ingenol mebutate?
   a. It has been approved for the treatment of squamous cell carcinoma.
   b. It has been approved for the treatment of basal cell carcinoma.
   c. It has been approved for the treatment of actinic keratosis.
   d. It has been approved for the treatment of malignant melanoma.

19. Which of the following types of adverse events are most likely to result from the use of ingenol mebutate?
   a. Gastrointestinal
   b. Dermatologic
   c. Neurologic
   d. Pulmonary

20. Which of the following statements is correct regarding glucarpidase?
   a. It rapidly converts methotrexate to inactive metabolites.
   b. It increases the rate of elimination of methotrexate via the kidneys.
   c. It should not be used within 48 hours of a dose of leucovorin.
   d. It is administered once a day for 8 days.

CPE information
To obtain 2.0 contact hours (0.2 CEUs) of CPE credit for this activity, you must complete the Assessment, the Learning Evaluation, and the Activity Evaluation. A Statement of Credit will be awarded for a passing grade of 70% or better on the Assessment. You will have two opportunities to successfully complete the CPE Assessment. Pharmacists who successfully complete this activity before November 1, 2015, can receive CPE credit. Your Statement of Credit will be available upon successful completion of the Assessment, Learning Evaluation, and Activity Evaluations and will be stored in your ‘My Training Page’ and on CPE Monitor for future viewing/printing.

CPE instructions:
1. Log in or create an account at pharmacist.com and select LEARN from the top of the page; select Continuing Education, then Home Study CPE to access the Library.
2. Enter the title of this article or the ACPE number to search for the article and click on the title of the article to start the home study.
3. To receive CPE credit, select Enroll Now from the left navigation and successfully complete the Assessment (with randomized questions), Learning Evaluation, and Activity Evaluation.
4. To get your Statement of Credit, click “Claim” on the right side of the page. You will need to provide your NABP e-profile ID number to obtain and print your Statement of Credit.

Live step-by-step assistance is available Monday through Friday from 8:30 am to 5:00 pm ET at APhA Member Services at 800-237-APhA (2742) or by e-mailing education@aphanet.com.