New therapeutic agents marketed in 2014: Part 4
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Abstract

Objective: To provide information on the most important properties of new therapeutic agents marketed in 2014.

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

Data synthesis: In the first, second, and third parts of this four-part series, 26 new therapeutic agents were reviewed (Pharmacy Today, October and November 2014; April 2015). In this fourth and concluding part of the series, 16 additional new therapeutic agents are covered, including 9 new antineoplastic agents. Both pembrolizumab and nivolumab treat unresectable or metastatic melanoma and disease progression following other therapies. Ceritinib is the second drug approved for anaplastic lymphoma kinase–positive, metastatic non–small cell lung cancer, joining crizotinib. Ramucirumab, initially approved for advanced or metastatic gastric adenocarcinomas, has been approved for additional indications. Olaparib is the first of a new class of drugs for ovarian cancer. Blinatumomab is an immunotherapy agent indicated for relapsed or refractory B-cell precursor acute lymphoblastic leukemia. Idelalisib was approved for three types of B-cell blood cancers, including chronic lymphocytic leukemia. Belinostat, a histone deacetylase inhibitor, is indicated for relapsed or refractory peripheral T-cell lymphoma. Siltuximab has been approved for multicentric Castleman disease, a rare lymphoproliferative blood disorder. The seven other new drugs in this review have been approved for the treatment of rare or uncommon disorders. Droxidopa, a prodrug of norepinephrine, is indicated for symptomatic neurogenic orthostatic hypotension. Pirfenidone and nintedanib are the first drugs to be approved for idiopathic pulmonary fibrosis. Eliglustat is the first orally administered drug approved as a first-line therapy for certain patients with Gaucher disease type 1. Elosulfase alfa is indicated for the treatment of mucopolysaccharidosis type IVA, a rare genetic lysosomal storage disorder. Metreleptin, a leptin analog, is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with generalized lipodystrophy. Miltefosine, an antiparasitic agent, has been approved for visceral, cutaneous, or mucosal leishmaniasis.

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Learning objectives

- Identify the new therapeutic agents and explain their appropriate use.
- Identify the indications, 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 for dosage and administration.
- Demonstrate appropriate counseling on use of the new medications and precautions to be observed.
Objective

In this fourth and concluding part of the series on new therapeutic agents marketed in 2014, 16 additional agents are covered, including 9 new antineoplastic agents: pembrolizumab, nivolumab, cetirizib, ramucirumab, olaparib, blinatumomab, idelalisib, belinostat, siltuximab, droxidopa, pirfenidone, nintedanib, eliglustat, elosulfase alfa, metreleptin, and miltifosine (Table 1).

Antineoplastic agents

Nine new antineoplastic agents—pembrolizumab, nivolumab, cetirizib, ramucirumab, olaparib, blinatumomab, idelalisib, belinostat, siltuximab, droxidopa, pirfenidone, nintedanib, eliglustat, elosulfase alfa, metreleptin, and miltifosine—are considered individually in the following sections.

Agents for melanoma

Melanoma is the most dangerous type of skin cancer and the leading cause of death from skin disease. According to the National Cancer Institute, approximately 76,000 Americans were diagnosed with melanoma in 2014, and almost 10,000 individuals died from the disease. If diagnosed early, melanoma is often curable. However, the prognosis for patients with late-stage (metastatic) melanoma is very poor. Until recently, the treatment options for patients with metastatic melanoma were very limited in both numbers and effectiveness.

In 2011, two important new drugs were marketed for the treatment of patients with metastatic melanoma. Ipilimumab (Yervoy) is a monoclonal antibody that binds to the cytotoxic T-lymphocyte–associated antigen–4 (CTLA-4). By blocking the action of CTLA-4, ipilimumab increases T-cell activation and proliferation; its benefit is thought to result from T-cell–mediated antitumor responses. It was the first drug demonstrated to prolong survival in patients with metastatic melanoma.

A protein designated as BRAF is an important component of a pathway involved in normal cell growth and survival. Mutations that keep the BRAF protein in an active state may cause excessive signaling in the pathway, resulting in uncontrolled cell growth. These mutations, most often BRAF V600 mutations, occur in approximately one-half of melanomas. An estimated 85% of these mutations are of the V600E type, and 10% are of the V600K type.

In late 2011, vemurafenib (Zelboraf), a BRAF kinase inhibitor, was marketed for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation. Although many patients experienced benefit with vemurafenib, it was often of a brief duration, a response that was attributed to the development of resistance involving mitogen-activated extracellular signal-regulated kinase (MEK) pathways.

Advances in the treatment of metastatic melanoma continued in 2013 with the marketing of trametinib (Mekinist), a MEK inhibitor, as well as dabrafenib (Tafinlar), which has properties that are most similar to those of vemurafenib. These two drugs were initially approved for use as individual agents but were subsequently approved for use together in a regimen that increases and extends the clinical benefit for some patients.

Pembrolizumab (Keytruda—Merck) and nivolumab (Opdivo—Bristol–Myers Squibb) were FDA approved in September and December 2014, respectively. Both agents are humanized monoclonal antibodies that have a novel, but essentially similar, mechanism of action to block the programmed death receptor–1 (PD-1) protein. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to the inhibition of active T-cell immune surveillance of tumors. The two new agents bind to the PD-1 receptor and block its interaction with PD-L1 and PD-L2, releasing PD-1 pathway–mediated inhibition of the immune response, including the antitumor immune response.

Both pembrolizumab and nivolumab are administered by I.V. infusion and were approved for the same indication: the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation–positive, a BRAF inhibitor. Both drugs were approved under the provisions of FDA’s accelerated approval program on the basis of tumor response rate and durability of response. FDA also granted both agents breakthrough therapy designation because preliminary clinical evidence suggested a potential for substantial improve-
T he most serious concerns associated with use of pembrolizumab and nivolumab are immune-mediated adverse events, which were experienced by a small number of patients in the clinical studies. These include pneumonitis, colitis, hepatitis, nephritis, hypophysitis, hypothyroidism, and hypothyroidism. Corticosteroids may be used to treat these events depending on the severity of the reaction; for some patients, however, it may be necessary to withhold or permanently discontinue treatment with the new drug. Of the immune-mediated adverse events, hypothyroidism was most commonly experienced (8% with each agent). Patients should be monitored for changes in thyroid function. Most patients who experience hypothyroidism can be successfully treated with thyroid hormone replacement therapy.

Pembrolizumab and nivolumab may cause harm to an unborn child if administered during pregnancy. Women of childbearing potential should be advised to use highly effective contraception during treatment and for at least 4 months after the last dose of pembrolizumab and at least 5 months after the last dose of nivolumab. It is not known whether the two new drugs are excreted in human milk, and a decision should be made whether to discontinue breastfeeding or not use the drug.

Pembrolizumab was evaluated in a study in patients with advanced melanoma whose disease had progressed after prior treatment, in which the major efficacy outcome measure was overall response rate (ORR). In 89 patients who were treated with the new drug in the recommended dosage of 2 mg/kg, the ORR was 24%, and the duration of the response was at least 1.4 to 8.5 months.

Adverse events reported most often with use of pembrolizumab include fatigue (47%), nausea (30%), cough (30%), pruritus (30%), rash (29%), decreased appetite (26%), constipation (21%), diarrhea (20%), and arthralgia (20%).

Pembrolizumab is administered as an I.V. infusion over 30 minutes. The recommended dosage is 2 mg/kg every 3 weeks. The product labeling should be consulted for recommended treatment/dosage modifications when adverse events are experienced.

Pembrolizumab is supplied as a lyophilized powder in single-use vials containing 50 mg of the drug. The vials should be stored in a refrigerator. The vial contents are reconstituted with 2.3 mL of sterile water for injection by injecting it along the walls of the vial and not directly on the powder. The vial should be slowly swirled and should not be shaken. The volume of solution needed to provide the appropriate dose is withdrawn from the vial and transferred into an I.V. bag containing 0.9% sodium chloride injection. The diluted solution should be mixed by gentle inversion, and the final concentration should be between 1 mg/mL to 10 mg/mL.

Nivolumab was evaluated in a study of patients with advanced melanoma whose disease had progressed after prior treatment, in which the major efficacy outcome measure was ORR. The ORR was 32%, and the effect lasted for more than 6 months in approximately one-third of these patients.

On March 4, 2015, FDA expanded the approval of nivolumab to include the treatment of patients with metastatic squamous non–small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. The ORR was 15% for the patients in the study that was the basis for this additional indication.

Adverse events experienced most often in the study in which nivolumab was used for the treatment of patients with melanoma include rash (21%), pruritus (19%), and cough (17%).

### Table 1. New therapeutic agents marketed in the United States in 2014: Part 4

<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>Belinostat</td>
<td>Belodac</td>
<td>Spectrum</td>
<td>Antineoplastic</td>
<td>I.V.</td>
<td>1-P</td>
</tr>
<tr>
<td>Blinatumomab</td>
<td>Blincyto</td>
<td>Amgen</td>
<td>Antineoplastic</td>
<td>I.V.</td>
<td>Pc</td>
</tr>
<tr>
<td>Ceritinib</td>
<td>Zykadia</td>
<td>Novartis</td>
<td>Antineoplastic</td>
<td>Oral</td>
<td>1-P</td>
</tr>
<tr>
<td>Droxidopa</td>
<td>Northern</td>
<td>Lundbeck</td>
<td>Orthostatic hypotension</td>
<td>Oral</td>
<td>1-P</td>
</tr>
<tr>
<td>Eliglustat tartrate</td>
<td>Cerdelga</td>
<td>Genzyme</td>
<td>Gaucher disease</td>
<td>Oral</td>
<td>1-P</td>
</tr>
<tr>
<td>Elosulfase alfa</td>
<td>Vimizin</td>
<td>BioMarin</td>
<td>Mucopolysaccharidosis</td>
<td>I.V.</td>
<td>Pc</td>
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<tr>
<td>Idelalisib</td>
<td>Zydelig</td>
<td>Gilead Sciences</td>
<td>Antineoplastic</td>
<td>Oral</td>
<td>1-S</td>
</tr>
<tr>
<td>Metreleptin</td>
<td>Myalept</td>
<td>Bristol–Myers Squibb</td>
<td>Lipodystrophy</td>
<td>Subcutaneous</td>
<td>Pc</td>
</tr>
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<td>Miltefosine</td>
<td>Impavid</td>
<td>Knight</td>
<td>Antiparasitic</td>
<td>Oral</td>
<td>1-P</td>
</tr>
<tr>
<td>Nintedanib</td>
<td>Olve</td>
<td>Boehringer Ingelheim</td>
<td>Pulmonary fibrosis</td>
<td>Oral</td>
<td>1-P</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Opdivo</td>
<td>Bristol–Myers Squibb</td>
<td>Antineoplastic</td>
<td>I.V.</td>
<td>Pc</td>
</tr>
<tr>
<td>Olaparib</td>
<td>Lynparza</td>
<td>AstraZeneca</td>
<td>Antineoplastic</td>
<td>Oral</td>
<td>1-P</td>
</tr>
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<td>Pembrolizumab</td>
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<td>Merck</td>
<td>Antineoplastic</td>
<td>I.V.</td>
<td>Pc</td>
</tr>
<tr>
<td>Pirfenidone</td>
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<td>InterMune</td>
<td>Pulmonary fibrosis</td>
<td>Oral</td>
<td>1-P</td>
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<tr>
<td>Ramucirumab</td>
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<td>Lilly</td>
<td>Antineoplastic</td>
<td>I.V.</td>
<td>Pc</td>
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<tr>
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<td>Janssen Biotech</td>
<td>Antineoplastic</td>
<td>I.V.</td>
<td>Pc</td>
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</tbody>
</table>

2. FDA classification of new drugs: 1 = new molecular entity; P = priority review; S = standard review.
3. A biological approved through an FDA procedure that does not assign a numerical classification.
Nivolumab is administered as an IV. infusion over 60 minutes. The recommended dosage is 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The product labeling should be consulted for the recommended treatment/dosage modifications when adverse events are experienced.

Nivolumab injection is supplied in single-use vials containing 40 mg (in 4 mL) and 100 mg (in 10 mL) of the drug. The vials should be stored in a refrigerator. The volume of solution needed to provide the appropriate dose is withdrawn from the vial and transferred into an IV. container, then diluted with either 0.9% sodium chloride injection or 5% dextrose injection to prepare an infusion with a final concentration in the range of 1 mg/mL to 10 mg/mL. The diluted solution should be mixed by gentle inversion and should not be shaken.

**Agent for lung cancer**

Lung cancer is the leading cause of cancer death in the United States. Approximately 85% of lung cancers are NSCLC, and the vast majority of patients with these cancers are diagnosed with metastatic or advanced disease with a very poor prognosis. Up to 5% of patients with NSCLC, typically non-smokers, have a translocation of the anaplastic lymphoma kinase (ALK) gene, which can contribute to increased cell proliferation and survival in tumors expressing these proteins.

Crizotinib (Xalkori), an inhibitor of receptor tyrosine kinases, including ALK, was the first drug (marketed in 2011) targeted at the translocations within the ALK gene in patients diagnosed with NSCLC. Ceritinib (Zykadia—Novartis), a tyrosine kinase inhibitor approved in April 2014, is indicated for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant of crizotinib. The new drug was approved under the provisions of FDA’s accelerated approval program on the basis of tumor response rate and duration of response. An improvement in disease-related symptoms or survival has not been established.

Ceritinib was evaluated in a clinical trial with 163 patients, in which the major efficacy outcome measure was objective response rate (ORR). Approximately 50% of the patients experienced a partial response and 1% experienced a complete response, with the responses lasting an average of about 7 months.

The adverse events reported most frequently by patients in the clinical trial include diarrhea (86%), nausea (80%), vomiting (60%), abdominal pain (54%), constipation (29%), fatigue (52%), decreased appetite (34%), and elevated liver enzymes.

Almost all patients experienced at least one gastrointestinal (GI) adverse event, and 14% had severe reactions. Antidiarrheal agents, antiemetic agents, and/or fluid replacement have been beneficial to some patients, but if symptoms persist, it may be necessary to interrupt or discontinue treatment with ceritinib.

Interstitial lung disease (ILD)/pneumonitis, which may be life threatening, occurred in 4% of the patients in the clinical trial. Patients should be monitored closely for pulmonary symptoms, and ceritinib should be discontinued if ILD/pneumonitis symptoms are considered treatment-related.

Ceritinib may cause prolongation of the QT interval of the ECG, and its use is best avoided in patients with congenital long QT syndrome. In patients with congestive heart failure, bradycardia, or electrolyte abnormalities or in those who are taking other medications known to prolong the QT interval, ECGs and electrolytes should be monitored periodically. Because ceritinib may cause bradycardia, heart rate and blood pressure should be monitored regularly.

Liver function tests should be determined at least monthly and serum glucose concentrations as clinically indicated. Significant hyperglycemia has occurred with use of ceritinib, and it may be necessary to initiate antidiabetic therapy or adjust existing therapy.

Ceritinib may cause harm to an unborn child if administered during pregnancy and is classified in Pregnancy Category D. Women of childbearing potential should be advised to use effective contraception during treatment and for at least 2 weeks following completion of therapy. Although it is not known whether ceritinib is excreted in human milk, women taking the drug should discontinue breastfeeding.

Exposure of ceritinib is increased significantly when it is administered with a meal. This may increase the risk of adverse events; therefore, the drug should be administered on an empty stomach (i.e., not within 2 h of a meal). Ceritinib demonstrates pH-dependent solubility, and concurrent use of a gastric acid suppressive agent (e.g., antacids, proton pump inhibitors) may reduce its solubility and bioavailability.

Ceritinib is a substrate of cytochrome P450 (CYP)3A and P-glycoprotein (P-gp). More than 90% of a dose is recovered in the feces, primarily in its unchanged form. The exposure of ceritinib is not likely to be significantly affected in patients with mild hepatic impairment. However, information on its use in patients with moderate or severe hepatic impairment is very limited. Ceritinib’s action may be increased by strong CYP3A inhibitors (e.g., clarithromycin) and decreased by strong CYP3A inducers (e.g., carbamazepine, rifampin, St. John’s wort); concurrent use of these agents should be avoided.

Grapefruit and grapefruit juice may also inhibit CYP3A and should be avoided by patients treated with ceritinib. If use of a strong CYP3A inhibitor can’t be avoided, the dosage of ceritinib should be reduced by approximately one-third, rounded to the nearest 150-mg dosage strength.

Because ceritinib may inhibit CYP3A and CYP2C9, concurrent use of medications that are substrates of these pathways and have narrow therapeutic indices (e.g., CYP3A substrates cyclosporine, fentanyl; CYP2C9 substrates phenytoin, warfarin) should be avoided.

The recommended dosage of ceritinib is 750 mg once a
day at least 2 hours apart from a meal, until disease progression or unacceptable toxicity. If a dose is missed, it should be taken as soon as possible unless the next dose is due within 12 hours. The product labeling should be consulted for recommended treatment/dosage modifications in the event of adverse reactions or use of potentially interacting drugs. Approximately 60% of patients for whom treatment was initiated with the recommended dosage required at least one dosage reduction, and the median time to the first dosage reduction was 7 weeks.

Ceritinib capsules are supplied in a 150-mg potency.

Agent for gastric cancer

In 2014, approximately 22,000 Americans were diagnosed with stomach cancer, and 11,000 individuals with this disease died. It is more prevalent in countries outside the United States and Europe and is the fifth most common cancer in the world. The cancer develops slowly and most often affects older adults. The most common type of stomach cancer is adenocarcinoma, which starts in one of the common cell types found in the lining of the stomach. The antineoplastic agents most often used in the treatment of gastric cancers include fluoropyrimidine- or platinum-containing chemotherapy, irinotecan, docetaxel, or paclitaxel, or combinations of these agents.

Ramucirumab (Cyramza—Lilly), administered by I.V. infusion, is a human monoclonal antibody that acts as a vascular endothelial growth factor receptor 2 antagonist that is thought to inhibit angiogenesis and reduce the blood supply to tumors. Ramucirumab was initially approved in April 2014 for use as a single agent for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy, irinotecan, docetaxel, or paclitaxel, or combinations of these agents.

Ramucirumab (Cyramza—Lilly), administered by I.V. infusion, is a human monoclonal antibody that acts as a vascular endothelial growth factor receptor 2 antagonist that is thought to inhibit angiogenesis and reduce the blood supply to tumors. Ramucirumab was initially approved in April 2014 for use as a single agent for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy, irinotecan, docetaxel, or paclitaxel, or combinations of these agents.

Ramucirumab was initially approved in April 2014 for use as a single agent for the treatment of patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after fluoropyrimidine- or platinum-containing chemotherapy, irinotecan, docetaxel, or paclitaxel, or combinations of these agents.

Its effectiveness was evaluated in a study in which patients received ramucirumab plus best supportive care or placebo plus best supportive care. The major efficacy outcome measure was overall survival, and patients treated with ramucirumab experienced a median overall survival of 5.2 months compared with 3.8 months in patients receiving placebo. In addition, patients treated with the new drug experienced a delay in tumor growth (progression-free survival).

In November 2014, FDA extended this indication for ramucirumab by approving its use in combination with paclitaxel. This action was based on the results of a study in which patients treated with ramucirumab plus paclitaxel experienced a median overall survival of 9.6 months, compared with 7.4 months in patients treated with placebo plus paclitaxel.

The labeled indications for ramucirumab were extended further in December when FDA approved its use, in combination with docetaxel, for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. In the study supporting approval of this indication, patients treated with ramucirumab plus docetaxel experienced a median overall survival of 10.5 months, compared with 9.1 months in patients treated with placebo plus docetaxel.

The most important concern with use of ramucirumab is the risk of hemorrhage, which may be fatal. The incidence of severe bleeding was 3.4% in the study in which ramucirumab was used as a single-agent treatment, and this risk is the subject of a boxed warning in its labeling. Other serious events that have been reported include GI perforation, arterial thromboembolic events (e.g., myocardial infarction), impaired wound healing, clinical deterioration in patients with cirrhosis, reversible posterior leukoencephalopathy syndrome, hypertension, and infusion-related reactions.

The most frequently experienced adverse events in the clinical study in which ramucirumab was used as a single-agent treatment include hypertension (16%) and diarrhea (14%). In the study in which it was used in combination with paclitaxel, the adverse events reported most often were fatigue (57%), neutropenia (54%), diarrhea (32%), epistaxis (31%), hypertension (25%), and peripheral edema (25%).

Severe hypertension occurred in 8% and 15% of patients, respectively, in the two studies, and blood pressure should be monitored every 2 weeks during treatment or more frequently as indicated.

Ramucirumab may cause harm to an unborn child if administered during pregnancy. Women of childbearing potential should be advised to use effective contraception during treatment and for at least 3 months following the last dose of the drug. It is not known whether the drug is excreted in human milk, and a decision should be made whether to discontinue breastfeeding or not use the drug.

Ramucirumab is administered by I.V. infusion over 60 minutes. In the treatment of patients with gastric cancer, the recommended dosage is 8 mg/kg every 2 weeks. If paclitaxel is used in combination, it is administered every week, and ramucirumab should be administered prior to paclitaxel. Before each infusion of ramucirumab, patients should be pretreated with an I.V. antihistamine (e.g., diphenhydramine). For patients who have experienced a Grade 1 or 2 infusion-related reaction, dexamethasone (or an equivalent corticosteroid) and acetaminophen should also be administered before each infusion.

The product labeling should be consulted for recommended treatment/dosage modifications in patients who experience adverse events, as well as for dosage recommendations for patients with NSCLC. Dosage adjustments are not necessary in patients with renal impairment or mild hepatic impairment. Treatment with ramucirumab may be continued until disease progression or unacceptable toxicity.

Ramucirumab injection is supplied in single-use vials containing 100 mg (in 10 mL) and 500 mg (in 50 mL) of the drug. The vials should be stored in a refrigerator. The volume of solution needed to provide the calculated dose should be withdrawn from the vial(s) and diluted with only 0.9% sodium chloride injection in an I.V. infusion container.
to a final volume of 250 mL. The infusion solution should be gently inverted to ensure adequate mixing.

**Agent for ovarian cancer**

Approximately 22,000 women in the United States were diagnosed with ovarian cancer in 2014, and more than 14,000 women with this disease died during the year. Ovarian cancer is often diagnosed late; more than 60% of women have already experienced metastasis by the time of diagnosis. As a consequence, the prognosis is very poor, with a 5-year survival rate of only 27%.

In up to 15% of women with ovarian cancer, the disease is associated with defective BRCA genes. The BRCA genes are involved in repairing damaged DNA and normally work to suppress tumor growth. A BRCA mutation is the most common cause of homologous repair deficiency. In BRCA-mutated tumor cells, homologous recombination is defective, and DNA double-strand break repair is forced to occur via error-prone pathways, which can lead to genomic instability and cell death.

Olaparib (Lynparza—AstraZeneca) has been approved for use as monotherapy in patients with deleterious or suspected deleterious germline BRCA–mutated (gBRCAm; as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The new drug was approved under the provisions of FDA’s accelerated approval program.

Olaparib, an inhibitor of polyadenosine 5′-diphosphoryl-bose (poly(ADP-ribose) polymerase (PARP) enzymes, is the first of a new class of drugs for the treatment of ovarian cancer. PARP enzymes are involved in normal cellular homoeostasis such as DNA transcription and DNA repair. Olaparib appears to inhibit growth of select tumor cell lines, and increased cytotoxicity and antitumor activity were noted in cell lines with deficiencies in BRCA.

Efficacy of olaparib was evaluated in a study of 137 patients with gBRCAm-associated ovarian cancer that was designed to measure ORR. Thirty-four percent of the patients experienced a response (complete response, 2%; partial response, 32%) for an average of 79 months. BRCA mutations in patients’ blood samples were detected using a genetic test (BRACAnalysis CDx) that FDA approved as a companion diagnostic concurrent with the approval of olaparib.

Myelodysplastic syndrome/acute myeloid leukemia has been reported (2% incidence) with use of olaparib and has been fatal for some patients. Treatment with olaparib should not be initiated until patients have recovered from hematological toxicity caused by previous chemotherapy. Complete blood counts should be determined at baseline and at least monthly thereafter. Pneumonitis has also occurred (<1%); if patients experience new or worsening respiratory symptoms (e.g., dyspnea, cough), treatment should be interrupted to permit evaluation. If pneumonitis is confirmed, treatment should be discontinued.

The most common adverse events experienced in the clinical study include fatigue/asthenia (66%), nausea (64%), vomiting (43%), abdominal pain/discomfort (43%), anemia (45%), diarrhea (31%), nasopharyngitis/pharyngitis/upper respiratory infection (26%), dyspepsia (25%), decreased appetite (22%), myalgia (22%), and arthralgia/musculoskeletal pain (21%). Many patients in the clinical study experienced laboratory abnormalities, including decreases in hemoglobin (anemia; 90%), lymphocytes (lymphopenia; 56%), platelets (thrombocytopenia; 30%), and absolute neutrophil count (neutropenia; 25%), and increases in creatinine (30%).

Olaparib may cause harm to an unborn child if administered during pregnancy and is classified in Pregnancy Category D. Women of childbearing potential should be advised to use effective contraception during treatment and for 1 month following the last dose of olaparib.

Olaparib is a substrate of CYP3A4, and most of its metabolism occurs via this pathway. Most of a dose is eliminated in the form of metabolites, almost equally in the urine (44%) and feces (42%). Dosage adjustment is not necessary in patients with mild renal impairment. However, no data are available on patients with moderate or severe renal impairment or those with hepatic impairment.

The concentration and action of olaparib may be increased by strong (e.g., clarithromycin, itraconazole) or moderate (e.g., diltiazem, fluconazole) inhibitors of CYP3A, and concurrent use should be avoided. If concurrent use of these agents is considered necessary, the dosage of olaparib should be reduced. Grapefruit and Seville oranges should also be avoided during olaparib treatment. The action of olaparib may be decreased by strong (e.g., carbamazepine, rifampin, St. John’s worth) and moderate (e.g., efavirenz) CYP3A inducers, and concurrent use should be avoided.

Olaparib capsules are supplied in a 50-mg potency. Following confirmation of the BRAC mutations with the FDA-approved test, treatment is initiated with the recommended dosage of 400 mg (eight 50-mg capsules) twice a day. The drug may be administered without regard to food, and the capsules should be swallowed whole and not opened, chewed, or dissolved. If a dose is missed, the patient should take the next dose at the scheduled time. Treatment should be continued until disease progression or unacceptable toxicity.

If adverse events occur, the dosage should be reduced to 200 mg twice a day and, if a further dosage reduction is necessary, to 100 mg twice a day. If concomitant use of a CYP3A inhibitor is necessary, the dosage of olaparib should be reduced to 150 mg twice a day if a strong CYP3A inhibitor is used and to 200 mg twice a day if a moderate CYP3A inhibitor is used.

**Agent for acute lymphoblastic leukemia**

An estimated 6,000 Americans were diagnosed with acute lymphoblastic leukemia (ALL) in 2014, and almost 1,500 individuals with this disease died during the year. Adult ALL most often occurs in young adults, with a median age at diagnosis of 34 to 39 years. Patients with relapsed or refractory ALL have a median overall survival of just 3 to 5 months.

Blinatumomab (Blincyto—Amgen) is an immunotherapy
administered by continuous IV infusion for the treatment of patients with Philadelphia chromosome–negative relapsed or refractory B-cell precursor ALL (B-cell ALL). Precursor B-cell ALL is an uncommon but rapidly growing form of cancer of the blood and bone marrow in which the body makes too many B-cell lymphoblasts, an immature type of white blood cell. The Philadelphia chromosome is an abnormality that sometimes occurs in the bone marrow cells of patients with leukemia.

Blinatumomab uses certain parts of a patient’s immune system to fight diseases such as cancer and is designated as a bispecific CD19-directed CD3 T-cell engager (BiTE) antibody construct product. It binds to CD19, a protein found on the surface of most B-cell lymphoblasts, and acts as a connector between CD19 and CD3, which is expressed on the surface of T cells. The modified antibody is designed to engage two different targets simultaneously, thereby juxtaposing T cells, which are capable of killing other cells perceived as threats, with cancer cells. BiTE antibody constructs help place the T cells within reach of the targeted cell, with the intent of allowing T cells to inject toxins and trigger the cancer cell to die (apoptosis).

Because of its unique mechanism of action and potential value in the treatment of patients with conditions such as leukemias, FDA designated blinatumomab as a breakthrough therapy and approved it under the agency’s accelerated approval program.

Effectiveness of blinatumomab was evaluated in a study of 185 patients. Of the patients who were treated with the drug for at least 4 weeks, 32% experienced a complete remission for a median of 6.7 months.

Use of blinatumomab is contraindicated in patients with known hypersensitivity to the drug or to any component of its formulation. The most important concerns associated with its use are the risks of cytokine release syndrome and neurological toxicities, both of which may be life threatening and are the subjects of boxed warnings in its labeling.

Cytokine release syndrome includes manifestations such as pyrexia, asthenia, hypotension, elevated liver function tests, and, in some patients, disseminated intravascular coagulation and capillary leak syndrome.

Neurological toxicities have included confusion, disorientation, coordination and balance disorders, convulsions, disturbances in consciousness, and encephalopathy. Patients should avoid driving and engaging in hazardous occupations or activities while the drug is being administered.

Other serious problems that have been reported with the use of blinatumomab include neutropenia, febrile neutropenia, infection, tumor lysis syndrome, leukoencephalopathy, and elevated liver function tests. Patients must be closely monitored with respect to these risks. The procedures for preparing and administering blinatumomab are complex, and caution must be exercised to avoid errors.

Adverse events experienced most frequently in the clinical study include pyrexia (62%), headache (36%), peripheral edema (25%), febrile neutropenia (25%), nausea (25%), hy-

Blinatumomab is administered by continuous IV infusion, and patients should be hospitalized for the first 9 days of the first cycle and the first 2 days of the second cycle. For all subsequent cycle starts and reinitiation (e.g., if treatment is interrupted for at least 4 h), supervision by a health professional or hospitalization is recommended. A single cycle of treatment consists of 4 weeks of continuous IV infusion followed by a 2-week treatment-free interval. Patients should be premedicated with dexamethasone 20 mg intravenously 1 hour before the first dose of each cycle, before an increase in dosage, or when restarting an infusion after an interruption of 4 or more hours.

For patients weighing at least 45 kg, the recommended dosage of blinatumomab is 9 mcg/day on days 1 through 7 of cycle 1, followed by 28 mcg/day on days 8 through 28. For subsequent cycles, the dosage is 28 mcg/day on days 1 through 28. A period of at least 2 treatment-free weeks should separate cycles of treatment. A course of treatment consists of up to two cycles of blinatumomab for induction followed by three additional cycles for consolidation treatment (up to a total of five cycles).

The product labeling should be consulted for recommended treatment/dosage modifications in patients who experience serious adverse events, as well as for the procedures and recommendations for preparing and administering blinatumomab infusions.

Blinatumomab is supplied as a lyophilized powder in single-use vials containing 35 mcg of the drug. The vials should be stored in a refrigerator. The package that contains the vial with the medication also includes a vial of IV solution stabilizer that is used to coat the prefilled IV. bag containing 0.9% sodium chloride injection before addition of reconstituted blinatumomab to prevent adhesion of the drug to IV. bags and IV. lines. IV. solution stabilizer contains citric acid monohydrate, lysine hydrochloride, and polysorbate 80 and must not be used for reconstitution of blinatumomab.

Agent for chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is a slowly worsening cancer of the blood and bone marrow that primarily affects older adults. Antineoplastic agents used in the treatment of CLL include chlorambucil, cyclophosphamide, fludarabine, bendamustine (Treanda), alemtuzumab, rituximab, ofatumumab (Arzerra), obinutuzumab (Gazyva), and ibrutinib (Imbruvica).

Several recent important advances have occurred in the treatment of CLL. In November 2013, obinutuzumab, the first drug designated by FDA as a breakthrough therapy, was approved in combination with chlorambucil for the treatment of patients with previously untreated CLL. Ofatumumab was initially approved in 2009 for the treatment of patients with CLL refractory to fludarabine and alemtuzumab. In April 2014 it was subsequently approved and designated as a breakthrough therapy for use in combination with chloram-
Idelalisib (Zydelig—Gilead Sciences) was approved in July 2014 for the treatment of patients with three types of B-cell blood cancers, including CLL, for which FDA designated it a breakthrough therapy. It is specifically indicated for use, in combination with rituximab, for the treatment of patients with relapsed CLL for whom rituximab alone would be considered appropriate therapy due to other comorbidities.

The new drug has also been approved for use as monotherapy in patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior systemic therapies, and for patients with relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies. The indications for FL and SLL were approved under the provisions of FDA’s accelerated approval program on the basis of ORR in the clinical studies.

Idelalisib is metabolized primarily via CYP3A and aldehyde oxidase, and almost 80% of the drug and its major metabolite are excreted in the feces. Dosage adjustment is not necessary in patients with a creatinine clearance of at least 15 mL/min.

Idelalisib tablets are supplied in 100-mg and 150-mg presentations.

The recommended dosage of idelalisib is 150 mg twice a day. The product labeling should be consulted for recommended treatment/dosage modifications if serious adverse events occur. Treatment with idelalisib should be continued until disease progression or unacceptable toxicity.

Idelalisib tablets are supplied in 100-mg and 150-mg presentations.

Agent for peripheral T-cell lymphoma
Peripheral T-cell lymphoma (PTCL), comprising a group of rare and aggressive non-Hodgkin lymphomas (NHLs) that develop from mature T cells, occurs in approximately 10,000 patients each year in the United States and represents 10% to 15% of NHLs.

Although several antineoplastic agents (e.g., cyclophosphamide, doxorubicin) have been used in the treatment of PTCL, the folate analog pralatrexate (Folotyn) was the first...
drug approved (in 2009) for the treatment of patients with this disease, although its specific indication is for patients with relapsed or refractory PTCL. Subsequently, the histone deacetylase (HDAC) inhibitor romidepsin (Istodax) has been approved for the treatment of PTCL in patients who have received at least one prior therapy.

Belinostat (Beleodaq—Spectrum), which was approved under the provisions of FDA's accelerated approval program, is administered by I.V. infusion for the treatment of patients with relapsed or refractory PTCL. Like romidepsin, as well as vorinostat (Zolinza), which is indicated for the treatment of patients with cutaneous T-cell lymphoma, it acts as a HDAC inhibitor. Its effectiveness was demonstrated in a clinical trial in patients with relapsed or refractory PTCL in which the ORR was 26%, representing a complete response in 11% of patients and a partial response in 15%. The median duration of response was 8.4 months.

The most frequently reported adverse events in the clinical study of belinostat include nausea (42%), fatigue (37%), pyrexia (35%), anemia (32%), and vomiting (29%). Nineteen percent of patients discontinued treatment because of adverse events. In addition to anemia, thrombocytopenia (16%), neutropenia, and lymphopenia have been experienced by some patients. Blood counts should be monitored weekly during treatment and appropriate dosage modifications made as necessary. Serious infections have been associated with the use of belinostat, and the drug should not be administered to patients with an active infection.

Liver function test abnormalities and hepatotoxicity have been reported with belinostat, and liver function tests should be monitored before treatment and before each cycle of treatment. Tumor lysis syndrome has also been experienced; patients with advanced stage disease and/or high tumor burden are at greatest risk and should be closely monitored.

Belinostat may cause harm to an unborn child if administered during pregnancy and is classified in Pregnancy Category D. Women of childbearing potential should be advised to use effective contraception while undergoing treatment with the drug. It is not known whether belinostat is excreted in human milk, and a decision should be made whether to discontinue breastfeeding or not use the drug.

Belinostat undergoes extensive hepatic metabolism, primarily by UGT1A1, and the concurrent use of a strong UGT1A1 inhibitor would be expected to increase exposure to the drug. Approximately 40% of a dose of belinostat is excreted renally, and less than 2% is recovered unchanged in the urine. Exposure to belinostat is increased in patients with impaired hepatic function, and patients with moderate and severe hepatic impairment were excluded from the clinical trials. There are insufficient data to recommend a dose in these patients and also in patients with renal impairment with a creatinine clearance of 39 mL/minute or less.

UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity, such as the UGT1A1*28 polymorphism. Approximately 20% of the black population, 10% of the white population, and 2% of the Asian population are homozygous for the UGT1A1*28 allele. Because clearance of belinostat is reduced in these patients, a lower dosage should be used.

Belinostat is administered by I.V. infusion over 30 minutes. The recommended dosage is 1,000 mg/m² once a day on days 1–5 of a 21-day cycle. The initial dosage should be reduced to 750 mg/m² in patients known to be homozygous for the UGT1A1*28 allele. Cycles can be repeated every 21 days until disease progression or unacceptable toxicity. The product labeling should be consulted for recommended treatment/dosage modifications if serious adverse events are experienced.

Belinostat is supplied as a lyophilized powder in single-use vials containing 500 mg of the drug. The contents of a vial are reconstituted by adding 9 mL of sterile water for injection that results in a concentration of 50 mg/mL. The volume of reconstituted solution needed to provide the required dosage should be withdrawn from the vials and transferred to an infusion bag containing 250 mL of 0.9% sodium chloride injection. If infusion site pain or other symptoms potentially attributable to the infusion occur, the infusion time may be extended to 45 minutes.

**Agent for Castleman disease**

Castleman disease is a rare lymphoproliferative blood disorder that is similar to lymphoma. Unicentric (localized) disease is the most common form and can often be cured with surgery, whereas multicentric Castleman disease (MCD) involves more than one group of lymph nodes at different anatomical sites. The most common manifestations of the disease, which usually affects adults, include fever, night sweats, weight loss, and fatigue.

The specific cause of MCD is not known, but it is thought to be associated with overproduction and release of interleukin–6 (IL-6) from activated B cells in affected lymph nodes. Other proinflammatory cytokines are also released. In many patients with MCD, human herpes virus 8 (HHV-8) appears to be associated with elevated concentrations of cytokines, particularly in patients who are HIV positive.

Siltuximab (Sylvant–Janssen Biotech), a chimeric monoclonal antibody that binds to IL-6 and is administered by I.V. infusion, is indicated for the treatment of patients with MCD who are HIV negative and HHV-8 negative. It is the first drug demonstrated to be effective in the treatment of MCD.

The drug was evaluated in a clinical trial of 79 participants in which patients received either siltuximab plus best supportive care or placebo plus best supportive care. The study’s major efficacy outcome was durable tumor and symptomatic response that persisted for a minimum of 18 weeks without treatment failure. This outcome was experienced by 34% of those receiving siltuximab, compared with 0% of those receiving placebo plus best supportive care.

Infusion-related reactions and hypersensitivity have been experienced with the use of siltuximab. If a mild to moderate infusion reaction occurs and is resolved, the infusion may be restarted at a slower infusion rate. For subsequent infusions,
its pharmacological effects through norepinephrine, not through the parent molecule or other metabolites. Norepinephrine increases blood pressure by inducing peripheral arterial and venous vasoconstriction.

Droxidopa is indicated for the treatment of orthostatic dizziness, lightheadedness, or “the feeling that you are about to black out” in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy.

Its effectiveness was demonstrated over a 2-week period in which patients reported a decrease in symptoms (e.g., dizziness, feeling faint). However, the duration of the improvement in patient symptoms has not been demonstrated for a period longer than 2 weeks, and the continued effectiveness of the drug should be assessed periodically.

FDA approved droxidopa under the provisions of its accelerated approval program.

Adverse events most often reported in the clinical studies include headache (13%), dizziness (10%), nausea (9%), and hypertension (7%). The most important concern with its use, included in a boxed warning, is the potential for supine hypertension and the increased risk of cardiovascular events (e.g., stroke). Supine blood pressure should be monitored before and during treatment, and more frequently when the dosage is increased. The risk of supine hypertension may be reduced by elevating the head of the bed, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, the dosage of droxidopa should be reduced or treatment discontinued. The risk of supine hypertension is increased by concurrent use of other medications that increase blood pressure.

Droxidopa may exacerbate existing ischemic heart disease, arrhythmias, and congestive heart failure, and the potential for these complications should be carefully considered prior to initiating treatment with the new drug. There have been infrequent postmarketing reports of a symptom complex (e.g., hyperpyrexia, confusion) that resembles neuroleptic malignant syndrome. Patients should be closely monitored for this possibility when the dosage of droxidopa is changed or when concomitant levodopa is reduced abruptly or discontinued, especially if the patient is receiving a neuroleptic agent.

The formulation of droxidopa contains FD&C Yellow No. 5 dye (tartrazine), which may cause allergic-type reactions in susceptible individuals. Tartrazine sensitivity is most often experienced by patients who also have aspirin hypersensitivity; caution should be observed when droxidopa is used in these individuals. Droxidopa is classified in Pregnancy Category C. It is probably excreted in breast milk, and a decision should be made whether to discontinue breastfeeding or not use the drug.

Droxidopa may be administered with or without food but should be administered in a consistent relationship with food. It crosses the blood brain barrier, and its metabolism...
Approximately 100,000 Americans have idiopathic pulmonary fibrosis (IPF), an irreversible disease caused by progressive scarring (fibrosis) of the lungs in which patients experience shortness of breath, cough, and difficulty participating in physical activities. The gradual destruction of lung tissue results in a reduced ability of the lungs to absorb oxygen and to transfer it to organs and tissues that require it to function properly. IPF usually occurs in adults over the age of 50, and the median survival time from diagnosis is approximately 3 years. Treatments have included oxygen therapy, pulmonary rehabilitation, and lung transplant.

FDA approved two drugs on the same date (October 15, 2014) as the first drugs demonstrated to be effective for the treatment of IPF. These drugs are considered individually in the following discussions.

Pirfenidone (Esbriet—InterMune), a pyridone derivative, is thought to act by interfering with the production of transforming growth factor–beta, a protein involved in how cells grow, and tumor necrosis factor–alpha. Its effectiveness was evaluated in three placebo-controlled trials in which the decline in forced vital capacity (FVC) was significantly reduced in patients treated with pirfenidone compared with those receiving placebo. However, results did not show a statistically significant difference in all-cause mortality between the drug and placebo groups.

The recommended initial dosage of pirfenidone is 100 mg three times a day upon arising in the morning, at midday, and in the late afternoon at least 3 hours before bedtime. The dosage should be titrated to symptomatic response in increments of 100 mg three times daily every 24 to 48 hours up to a maximum dosage of 600 mg three times a day. If a dose is missed, treatment should be continued with the next scheduled dose. Droxidopa capsules are supplied in 100-mg, 200-mg, and 300-mg potencies.

Agents for pulmonary fibrosis

Approximately 100,000 Americans have idiopathic pulmonary fibrosis (IPF), an irreversible disease caused by progressive scarring (fibrosis) of the lungs in which patients experience shortness of breath, cough, and difficulty participating in physical activities. The gradual destruction of lung tissue results in a reduced ability of the lungs to absorb oxygen and to transfer it to organs and tissues that require it to function properly. IPF usually occurs in adults over the age of 50, and the median survival time from diagnosis is approximately 3 years. Treatments have included oxygen therapy, pulmonary rehabilitation, and lung transplant.

FDA approved two drugs on the same date (October 15, 2014) as the first drugs demonstrated to be effective for the treatment of IPF. These drugs are considered individually in the following discussions.

Pirfenidone (Esbriet—InterMune), a pyridone derivative, is thought to act by interfering with the production of transforming growth factor–beta, a protein involved in how cells grow, and tumor necrosis factor–alpha. Its effectiveness was evaluated in three placebo-controlled trials in which the decline in forced vital capacity (FVC) was significantly reduced in patients treated with pirfenidone compared with those receiving placebo. However, results did not show a statistically significant difference in all-cause mortality between the drug and placebo groups.

Adverse events most often experienced in the clinical trials include nausea (36%), rash (30%), upper respiratory tract infection (27%), fatigue (25%), diarrhea (26%), abdominal pain (24%), headache (22%), dyspepsia (19%), dizziness (18%), vomiting (13%), anorexia (13%), gastroesophageal reflux disease (11%), sinusitis (11%), insomnia (10%), weight loss (10%), and arthralgia (10%).

Because the incidence of many of the adverse events was lower when pirfenidone was administered with food, doses of the drug should be administered with meals.

Photosensitivity reactions were reported by 9% of patients, so patients should be instructed to minimize or avoid exposure to sunlight, including sunlamps; to use a sunblock with an SPF of at least 50; to wear protective clothing; and to avoid other medications that cause photosensitivity. Some patients have experienced elevated liver enzymes, and ALT, AST, and bilirubin should be determined before initiating therapy, monthly for the first 6 months of therapy, and at least every 3 months thereafter.

Pirfenidone is primarily metabolized via the CYP1A2 pathway, and approximately 80% of a dose is excreted in the urine as the 5-carboxy metabolite. Caution should be exercised in patients with impaired hepatic or renal function. Because the new drug has not been evaluated in patients with severe hepatic impairment or in those with end-stage renal diseases requiring dialysis, its use in these patients is not recommended.

The systemic exposure and action of pirfenidone may be increased by the concurrent use of a strong (e.g., fluvoxamine) or moderate (e.g., ciprofloxacin) CYP1A2 inhibitor. Use of a strong CYP1A2 inhibitor should be discontinued before initiating treatment with pirfenidone, or if that is not feasible, the dosage of pirfenidone should be reduced. Smoking is an inducer of the CYP1A2 metabolic pathway, and the exposure of pirfenidone in smokers was significantly lower compared with nonsmokers. Smokers should be advised to discontinue smoking before initiating treatment with pirfenidone and to avoid smoking during treatment.

Pirfenidone capsules are supplied in a 267-mg potency. Doses should be administered with food at the same times each day. The dosage is titrated starting with one capsule (267 mg) three times a day on days 1 through 7, two capsules three times a day on days 8 through 14, and three capsules three times a day on days 15 and onward, which represents the maintenance dosage as well as the maximum recommended dosage. If a patient must be treated concurrently with a strong CYP1A2 inhibitor (e.g., fluvoxamine), the recommended maintenance dosage of pirfenidone is one capsule (267 mg) three times a day. If a moderate CYP1A2 inhibitor (e.g., ciprofloxacin) is used concurrently, the recommended maintenance dosage of pirfenidone is two capsules (534 mg) three times a day.

The product labeling should be consulted for recommended treatment/dosage adjustments for patients who experience adverse events (e.g., GI, hepatic).

Nintedanib (Ofev—Boehringer Ingelheim) inhibits multiple receptor tyrosine kinases (e.g., vascular endothelial growth factor receptor) that have been implicated in IPF pathogenesis. In addition, it inhibits certain nonreceptor tyrosine kinases, although whether this action contributes to efficacy in the treatment of IPF is not known.
Its effectiveness for patients with IPF was evaluated in three placebo-controlled trials in which the decline in FVC was significantly reduced in patients treated with the new drug compared with those receiving placebo. However, there was not a statistically significant difference in all-cause mortality between the drug and placebo groups.

The most frequently reported adverse events in the clinical trials include diarrhea (62%), nausea (24%), abdominal pain (15%), vomiting (12%), decreased appetite (11%), and weight loss (10%). Because most patients experience diarrhea, this response should be treated when it first develops, with adequate hydration and antidiarrheal medication (e.g., loperamide). GI adverse events have also included GI perforation, and the drug must be used with caution in patients who have had recent abdominal surgery.

Some patients treated with nintedanib have experienced arterial thromboembolic events (e.g., myocardial infarction), and caution must be exercised when treating patients at higher cardiovascular risk, including known coronary artery disease. Bleeding events were reported in 10% of the patients treated with nintedanib in the clinical studies, compared with 7% of those receiving placebo. The new drug should be used in patients with a known risk of bleeding (e.g., patients on anticoagulant therapy) only if the anticipated benefit outweighs the risk.

Elevated liver enzymes occurred in 14% of patients in the clinical studies. ALT, AST, and bilirubin should be determined before initiating treatment with nintedanib, monthly for 3 months, and at least every 3 months thereafter.

Nintedanib may cause harm to an unborn child if administered during pregnancy and is classified in Pregnancy Category D. Women of childbearing potential should use effective contraception during treatment and for at least 3 months following discontinuation of treatment. It is probable that the new drug and/or its metabolites are excreted in human milk, and a decision should be made whether to discontinue breastfeeding or not use the drug.

Following oral administration, the absolute bioavailability of nintedanib is approximately 5%. Exposure of the drug is increased by approximately 20% in the presence of food, and doses should be administered with food. Nintedanib is a substrate of P-glycoprotein (P-gp) and, to a minor extent, CYP3A4. The major route of elimination is fecal/biliary excretion, via which there is more than 90% recovery of a dose of the drug.

The safety of nintedanib has not been evaluated in patients with moderate and severe hepatic impairment, and its use in these patients is not recommended. The drugs have also not been studied in patients with severe renal impairment and end-stage renal disease. However, less than 1% of a dose of nintedanib is excreted via the kidney.

The action of nintedanib may be increased by a P-gp and CYP3A4 inhibitor (e.g., erythromycin), and concurrent use should be closely monitored. Conversely, its action may be reduced by a P-gp and CYP3A4 inducer (e.g., rifampin, carbamazepine, phenytoin, St. John’s wort), and concurrent use should be avoided. Smoking has been associated with decreased exposure to nintedanib, and patients should be encouraged to not smoke during treatment.

The recommended dosage of nintedanib is 150 mg twice a day with food approximately 12 hours apart. The product labeling should be consulted for the recommended treatment/dosage modifications if adverse events occur.

Nintedanib capsules are supplied in 100-mg and 150-mg potencies. The drug has a bitter taste, and the capsules should be swallowed whole, not chewed or crushed.

**Agent for Gaucher disease**

Gaucher disease is a rare genetic disease that is caused by a deficiency of acid beta-glucosidase (glucocerebrosidase), a lysosomal enzyme that catalyzes the conversion of the sphingolipid glucocerebroside into glucose and ceramide. This deficiency results in the accumulation of glucosylceramide, primarily in the lysosomal compartment of macrophages, giving rise to “Gaucher cells.” The Gaucher cells accumulate in the liver, spleen, and bone marrow, resulting in enlargement of the liver and spleen, as well as skeletal disease, anemia, and thrombocytopenia. Type 1 Gaucher disease is the most common type, affecting approximately 6,000 Americans.

Imiglucerase (Cerezyme), an analog of acid beta-glucosidase that represents enzyme replacement therapy for patients with type 1 Gaucher disease, has been the standard of treatment for approximately 20 years. Velaglucerase alfa (V Priv), marketed in 2010, and taliglucerase alfa (Elelyso), marketed in 2012, and their actions are essentially the same as that of imiglucerase. All three agents are administered by IV infusion.

The glucosylceramide synthase inhibitor miglustat (Zavesca) was marketed in 2003 as an oral treatment for patients with Gaucher disease. However, it is indicated only for adult patients with mild to moderate type 1 disease for whom enzyme replacement therapy is not a therapeutic option.

Eliglustat tartrate (Cerdelga—Genzyme) is indicated for the long-term treatment of adult patients with type 1 Gaucher disease who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs), as detected by an FDA-cleared test. Like miglustat, eliglustat is a glucosylceramide synthase inhibitor that acts as a substrate reduction therapy and is administered orally. However, the new drug is the only first-line oral treatment for certain patients with Gaucher disease.

Effectiveness of eliglustat was demonstrated in a placebo-controlled study in which the primary endpoint was the percentage change in spleen volume. Compared with placebo, treatment with eliglustat resulted in a greater reduction in spleen volume and also greater improvement in liver volume, hemoglobin concentrations, and platelet counts.

In a second study, eliglustat was compared with imiglucerase in patients who were previously treated and stabilized with imiglucerase or other enzyme replacement therapy. Treatment with the new drug resulted in similar stabiliza-
tion of hemoglobin concentration, platelet count, and spleen and liver volume as achieved with imiglucerase, and eliglustat was demonstrated to be noninferior to imiglucerase.

Adverse events most often experienced with eliglustat include fatigue (14%), headache (13%), nausea (12%), diarrhea (12%), back pain (12%), pain in extremity (11%), and upper abdominal pain (10%). Eliglustat may cause increases in intervals of the electrocardiogram (PR, QT, QRS), particularly at higher concentrations. Its use is not recommended in patients with preexisting cardiac disease (e.g., congestive heart failure, bradycardia, ventricular arrhythmia) or those with long QT syndrome, or in combination with Class IA (e.g., quinidine, procainamide) and Class III (e.g., amiodarone, sotalol) antiarrhythmic agents.

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

Eliglustat is extensively metabolized, primarily via the CYP2D6 pathway and to a lesser extent via the CYP3A4 pathway. Approximately 40% of a dose is excreted in the urine and 50% in the feces, mainly as metabolites. Dosage adjustment is not necessary in patients with mild renal impairment. However, the drug has not been studied in patients with moderate to severe renal impairment or in patients with any degree of hepatic impairment, and the drug is not recommended for use in these patients.

Because eliglustat is a CYP2D6 substrate, its activity is influenced by the patient’s CYP2D6 metabolizer status and concurrent use of a CYP2D6 inhibitor or inducer. An FDA-cleared test for determining CYP2D6 genotype should be used to determine a patient’s CYP2D6 metabolizer status. Patients who are CYP2D6 ultra-rapid metabolizers (URMs) may not attain a sufficient concentration of eliglustat to achieve a therapeutic effect. A specific dosage recommendation is not provided for patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers). Eliglustat is also a substrate for the CYP3A4 pathway and P-gp.

Use of eliglustat is contraindicated in patients who are CYP2D6 EMs and IMs and taking a strong (e.g., paroxetine) or moderate CYP2D6 inhibitor with a strong (e.g., itraconazole) or moderate (e.g., fluconazole) CYP3A inhibitor, and also in patients who are CYP2D6 IMs and PMs taking a strong CYP3A inhibitor. These drugs may increase the exposure and action of eliglustat and increase the risk of cardiovascular adverse events, including arrhythmias.

The product labeling should be consulted for recommended treatment/dosage modifications in patients who are also being treated with a CYP2D6 and/or CYP3A inhibitor. Because a strong CYP3A inducer (e.g., carbamazepine, rifampin, St. John’s wort) may significantly reduce the action of eliglustat, concurrent use is not recommended.

Eliglustat itself is an inhibitor of CYP2D6 and P-gp, and the product labeling should be consulted for information regarding potential interactions with other medications that are substrates for these pathways.

The recommended dosage of eliglustat is 84 mg twice a day in patients who are CYP2D6 EMs and IMs, and 84 mg once a day in patients who are CYP2D6 PMs. The predicted exposures with 84 mg once a day in patients who are CYP2D6 PMs are expected to be similar to exposures observed with 84 mg twice a day in patients who are CYP2D6 IMs.

Eliglustat capsules are supplied in an 84-mg potency. The capsules should be swallowed whole and may be administered with or without food; however, grapefruit products should be avoided because they inhibit the CYP3A pathway.

**Agent for mucopolysaccharidosis**

Mucopolysaccharidoses comprise a group of rare genetic lysosomal storage disorders caused by the deficiency of specific lysosomal enzymes required for the catabolism of glycosaminoglycans (GAGs). Mucopolysaccharidosis Type IVA (MPS IVA; Morquio A syndrome) is an autosomal recessive lysosomal storage disease characterized by the absence or marked reduction in N-acetylgalactosamine-6-sulfatase activity. The deficiency of this enzyme results in the accumulation of certain GAG substrates in the lysosomal compartment of cells, leading to widespread cellular, tissue, and organ dysfunction.

Onset of the disease occurs during childhood; the most common manifestations are problems with bone development, growth, pulmonary function, and mobility. Death often occurs in the second or third decade of life in patients with severe forms of the disease. There are approximately 800 patients with MPS IVA in the United States.

Elosulfase alfa (Vimizim—BioMarin) is a purified human enzyme, N-acetylgalactosamine-6-sulfatase, produced by recombinant DNA technology. This hydrolytic lysosomal GAG-specific enzyme is taken up into lysosomes and increases the catabolism of GAGs. Administered by IV infusion, it is the first drug approved for the treatment of patients with MPS IVA.

Effectiveness of eolsulfase alfa was evaluated in a placebo-controlled study of 176 patients who ranged in age from 5 to 57 years. The primary endpoint was the change from baseline in the distance walked in 6 minutes (6-min walk test) at week 24. On average, the patients treated with eolsulfase alfa walked 22.5 meters farther in 6 minutes compared with the patients who received placebo. One of the other endpoints included changes from baseline in the rate of stair climbing in 3 minutes. However, there was no difference in the rate of stair climbing between patients in the drug and placebo groups.

Many of the patients continued in an extension trial for an additional 48 weeks. In patients who continued to receive eolsulfase alfa, there was no further improvement in walking ability beyond what had been experienced in the first 24 weeks.

Hypersensitivity reactions including anaphylaxis have occurred with eolsulfase alfa and are the subject of a boxed
warning in its labeling. These reactions have occurred as early as 30 minutes from the start of an infusion but as late as 6 days after infusion. Patients with acute respiratory illness may be at risk of serious acute exacerbation of their respiratory compromise as a result of hypersensitivity reactions and require additional monitoring. Appropriate medical support should be readily available when the drug is administered, and patients should be closely observed for an appropriate period of time following administration. An antihistamine, with or without an antipyretic, should be administered prior to infusion.

Adverse events reported most often with the use of elosulfase alfa include pyrexia (33%), vomiting (31%), headache (26%), nausea (24%), abdominal pain (21%), chills (10%), and fatigue (10%). Elosulfase alfa is classified in Pregnancy Category C, and a registry (800-983-4587) collects data on pregnant women, as well as breastfeeding mothers, who are treated with the drug. Use of elosulfase alfa in children under 5 years of age has not been evaluated.

As with all therapeutic proteins, a potential for immunogenicity exists with elosulfase alfa. All patients in the placebo-controlled study developed antidrug antibodies by week 4, and all patients tested positive for neutralizing antibodies at least once during the trial. However, the relationship of these responses and the treatment effect and adverse events could not be determined.

Elosulfase alfa is administered by I.V. infusion over a minimum range of 3.5 to 4.5 hours on the basis of infusion volume. The recommended dosage is 2 mg/kg once a week. An antihistamine, with or without an antipyretic, should be administered 30 to 60 minutes before starting the infusion.

Elosulfase alfa injection is supplied in single-use vials containing 5 mg of the drug in a volume of 5 mL. The vials should be stored in a refrigerator. The volume of the injection needed to provide the calculated dose should be withdrawn from the vial(s) and diluted to a final volume of 100 mL or 250 mL with 0.9% sodium chloride injection. The final volume should be 100 mL for patients who weigh less than 25 kg and 250 mL for patients who weigh 25 kg or more. The product labeling should be consulted for information regarding administration of the drug.

Agent for lipodystrophy

Generalized lipodystrophy is a rare condition characterized by a lack or loss of fat (adipose) tissue. Patients with congenital generalized lipodystrophy are born with little or no adipose tissue, whereas individuals with acquired generalized lipodystrophy lose adipose tissue over time. The deficiency of adipose tissue leads to hypertriglyceridemia and ectopic deposition of fat in nonadipose tissues such as liver and muscle, contributing to metabolic abnormalities, including insulin resistance. Patients may experience severe insulin resistance at a young age and may have diabetes mellitus that is difficult to control and/or markedly elevated blood triglyceride concentrations that can result in inflammation of the pancreas.

The hormone leptin, produced in adipose tissue, regulates food intake and other hormones such as insulin and plays a major role in energy metabolism. Leptin deficiency that results from the loss of adipose tissue contributes to excess caloric intake, which exacerbates the metabolic abnormalities.

Metreleptin (Myalept—Bristol–Myers Squibb) is a recombinant methionyl–human leptin analog that binds to and activates leptin receptors. Administered by subcutaneous injection, it is indicated as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.

Metreleptin was evaluated in a study in 48 patients with generalized lipodystrophy who also had hypertriglyceridemia, diabetes, and/or elevated concentrations of fasting insulin. Patients experienced reductions in glycylated hemoglobin, glucose, and triglycerides within 4 months of treatment initiation.

Use of metreleptin has not been evaluated in patients with complications of partial lipodystrophy, HIV-related lipodystrophy, or liver disease, including nonalcoholic steatohepatitis. It has not been shown to be effective in treating general obesity, and its use is contraindicated in patients with general obesity not associated with congenital leptin deficiency.

There have been reports of the development of antilipodystrophy antibodies with neutralizing activity in patients treated with metreleptin. This could result in the loss of efficacy of the drug and inhibition of endogenous leptin action, as well as worsening metabolic control and/or severe infection. This is the subject of a boxed warning in the labeling for the drug. Patients who experience loss of efficacy or severe infection during treatment should be tested for anti-metreleptin antibodies with neutralizing activity.

Also included in the boxed warning is the risk of T-cell lymphoma, which has been experienced by some patients with acquired generalized lipodystrophy, both treated and not treated with metreleptin. The benefits and risks associated with the drugs should be carefully evaluated in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy.

Because of the serious risks associated with its use, metreleptin is available only through the Myalept Risk Evaluation and Mitigation Strategy (REMS) program. In this program, prescribers must receive training and be certified, and pharmacists must be certified and may dispense the drug only after receiving the appropriate authorization form for each new prescription.

Other risks associated with use of metreleptin include hypersensitivity reactions, exacerbation of autoimmune diseases, and hypoglycemia when used concomitantly with insulin or an insulin secretagogue (e.g., sulfonylureas). Blood glucose concentrations should be closely monitored in patients being treated concurrently with these agents, and a large reduction in insulin dosage or an insulin secretagogue may be necessary.
Adverse events reported most frequently in the clinical study of metreleptin include headache (13%), hypoglycemia (13%), decreased weight (13%), and abdominal pain (10%). The drug is classified in Pregnancy Category C and should be used during pregnancy only if the anticipated benefit justifies the risk to the unborn child. Women who become pregnant during treatment are encouraged to enroll in a program (855-6MYALEPT) that monitors outcomes in pregnant women. It is not known whether metreleptin is excreted in human milk, and a decision should be made whether to discontinue breastfeeding or not use the drug. Individuals participating in the clinical study of metreleptin included pediatric patients as young as 1 year of age.

Metreleptin is supplied as a solid, lyophilized cake in a vial that contains 11.3 mg of the drug and should be stored in a refrigerator. The drug is reconstituted with 2.2 mL of bacteriostatic water for injection (BWFI) or preservative-free water for injection (WFI) that provides a solution containing the drug in a 5-mg/mL concentration. When reconstituted with BWFI, the product contains benzyl alcohol, which has been associated with serious adverse events (e.g., “gassing syndrome”), particularly in neonates and low-birth-weight infants. Accordingly, preservative-free WFI is recommended when reconstituting the medication for use in neonates and infants.

Metreleptin is administered subcutaneously in the abdomen, thigh, or upper arm once a day at the same time every day, without regard to the timing of meals.

The recommended initial dosage in male patients weighing more than 40 kg is 2.5 mg once a day and in female patients weighing more than 40 kg, 5 mg once a day, with 10 mg the maximum daily dose in both male and female patients. In patients (male and female) weighing less than or equal to 40 kg, the recommended initial dosage is 0.06 mg/kg once a day. The product labeling should be consulted for additional information regarding dosage adjustments, as well as the preparation, administration, and storage of the medication.

**Antiparasitic agent**

Leishmaniasis, caused by the parasite *Leishmania* species, is transmitted to humans via bites of sand flies. The disease occurs primarily in people who live in countries in the tropics and subtropics. Patients in the United States who have the infection usually acquired it when they were living or traveling in a tropical country. The three main types of leishmaniasis are cutaneous, mucosal (affecting the nose and throat), and visceral (affecting internal organs). Treatment options are very limited, with liposomal amphotericin B the treatment of choice in the United States for patients with visceral leishmaniasis. Cutaneous and mucosal leishmaniasis have been treated with amphotericin B or oral azole antifungal drugs.

Miltefosine (Impavidol–Knight) was approved by FDA in 2014, although it has been available in other countries. Administered orally, the drug is specifically indicated in adults and adolescents 12 years of age and older who weighing at least 30 kg for the treatment of visceral leishmaniasis caused by *L. donovani*; cutaneous leishmaniasis caused by *L. braziliensis*, *L. guyanensis*, and *L. panamensis*; and mucosal leishmaniasis caused by *L. braziliensis*. It is the first drug to be approved in the United States for the treatment of cutaneous and mucosal leishmaniasis.

Effectiveness of miltefosine for the treatment of patients with visceral leishmaniasis was evaluated in a study in which it was compared with intravenously administered amphotericin B. An initial cure was achieved in 98% of the patients treated with each of the medications. When patients were evaluated again 6 months after treatment had been completed, the final cure rates were 94% and 97% for miltefosine and amphotericin B, respectively. In a placebo-controlled of patients treated with miltefosine for cutaneous leishmaniasis, 66% experienced a cure of the infection, compared with 30% of those receiving placebo. In a study in patients with mucosal leishmaniasis, 62% of the patients experienced a complete resolution of symptoms.

Efficacy of miltefosine against species of Leishmania other than those specifically studied in the clinical trials and identified in the labeled indications has not been evaluated. The clinical trial results and other experiences in the treatment of leishmaniasis also suggest a geographic variation in the clinical response of the same species of Leishmania.

Adverse events experienced most often in the largest clinical study with miltefosine (299 patients) include vomiting (38%), decreased appetite (23%), diarrhea (20%), elevations of transaminases (50%), creatinine elevations (10%), and thrombocytopenia (62%). Because vomiting and diarrhea may result in volume depletion, fluid intake should be encouraged. Doses of the drug should be administered with food to reduce the frequency and severity of GI adverse events. Renal function should be monitored weekly during therapy and for 4 weeks following completion of therapy, and liver transaminases, bilirubin, and platelet counts should be monitored during therapy.

Stevens–Johnson syndrome has been infrequently reported with the use of miltefosine; treatment should be discontinued if an exfoliative or bullous rash occurs during therapy. Miltefosine is contraindicated in patients with Sjogren–Larsson syndrome, which is caused by a genetic defect in fatty aldehyde dehydrogenase activity. The fatty alcohol–containing fragment of miltefosine can enter the metabolism of fatty acids after being metabolized to palmitic acid, and this oxidation is blocked in patients with Sjogren–Larsson syndrome.

Miltefosine may cause harm to an unborn child if administered during pregnancy, and this risk is the subject of a boxed warning in its labeling. It is classified in Pregnancy Category D, and its use is contraindicated during pregnancy. A urine or serum pregnancy test should be obtained before initiating treatment with the new drug. Women of childbearing potential should be instructed to use effective contraception during treatment and for 5 months after completion of
therapy. Because vomiting and/or diarrhea often occur during miltefosine treatment, the absorption and effectiveness of oral contraceptives may be reduced. If these GI adverse events occur, women should be advised to use additional nonhormonal or alternative method(s) of effective contraception.

It is not known whether miltefosine is excreted in human milk, and a decision should be made whether to discontinue breastfeeding or not use the drug. Breastfeeding should be avoided for 5 months following completion of miltefosine treatment.

Miltefosine should be administered with food and used over a treatment period of 28 consecutive days. The recommended dosage is 50 mg twice a day with breakfast and dinner in patients weighing 30 kg to 44 kg, and 50 mg three times a day with breakfast, lunch, and dinner in patients weighing 45 kg or greater.

Miltefosine capsules are supplied in a 50-mg potency.
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 reinforce the learning opportunity. There is only one correct answer to each question.

1. Which of the following drugs is administered three times a day?
   a. Olaparib
   b. Idelalisib
   c. Nintedanib
   d. Pirfenidone

2. Which of the following drugs should be administered apart from food?
   a. Miltefosine
   b. Ceritinib
   c. Nintedanib
   d. Pirfenidone

3. With use of which of the following agents should patients be monitored for changes in thyroid function?
   a. Belinostat
   b. Siltuximab
   c. Pembrolizumab
   d. Elosulfase alfa

4. Which of the following agents is administered by continuous I.V. infusion?
   a. Bblinatumomab
   b. Nivolumab
   c. Belinostat
   d. Ramucirumab

5. With use of which of the following agents is the determination of CYP2D6 metabolizer status important for patient selection and potential drug interactions?
   a. Metreleptin
   b. Elosulfase alfa
   c. Eliglustat
   d. Miltefosine

6. With use of which of the following agents should the last dose of the day be administered at least 3 hours before bedtime?
   a. Olaparib
   b. Idelalisib
   c. Nintedanib
   d. Droxidopa

7. For which of the following agents does the product labeling include a boxed warning on the risk of hemorrhage?
   a. Metreleptin
   b. Ramucirumab
   c. Belinostat
   d. Nivolumab

8. Which of the following statements is correct about pembrolizumab?
   a. It is classified as a BRAF inhibitor.
   b. It is indicated for the treatment of patients with gastric cancers.
   c. It is administered by bolus I.V. injection.
   d. It is administered every 3 weeks.

9. Which of the following statements is correct about nivolumab?
   a. It acts by binding to programmed death receptor-1 (PD-1) and blocking its interaction with PD-1 ligands.
   b. It is indicated for the treatment of certain ovarian cancers.
   c. It is administered subcutaneously.
   d. It is administered once every 28 days.

10. Which of the following statements is correct about ceritinib?
    a. It is classified as an enzyme replacement therapy.
    b. It is indicated for the treatment of patients with anaplastic lymphoma kinase–positive non–small cell lung cancer who have progressed on or are intolerant of crizotinib.
    c. Concurrent use with a CYP2D6 inhibitor should be avoided.
    d. It is administered twice a day.

11. Which of the following statements is correct about ramucirumab?
    a. It is classified as a tyrosine kinase inhibitor.
    b. It is indicated for the treatment of patients with acute lymphoblastic leukemia.
    c. Many patients experience hypertension with its use.
    d. When used in a combination regimen with paclitaxel, it should be administered following the administration of paclitaxel.

12. Which of the following statements is correct about olaparib?
    a. It acts as an inhibitor of poly ADP-ribose polymerase (PARP) enzymes.
    b. It is indicated for the treatment of patients with peripheral T-cell lymphoma.
    c. The concurrent use of a proton pump inhibitor may reduce its absorption and activity.
    d. It must be administered apart from food.
13. Which of the following statements is correct about blinatumomab?
   a. It is designated as a bispecific CD19-directed CD3 T-cell engager antibody construct product.
   b. It is indicated for the treatment of patients with chronic lymphocytic leukemia.
   c. It is used in combination with rituximab.
   d. It is administered every 4 weeks.

14. Which of the following statements is correct about idelalisib?
   a. It is classified as a histone deacetylase inhibitor.
   b. It is indicated for the treatment of patients with advanced or metastatic melanoma.
   c. Renal adverse events are commonly experienced, and renal function should be periodically monitored.
   d. Strong CYP3A inducers may reduce its action, and concurrent use should be avoided.

15. Which of the following statements is correct?
   a. Belinostat is indicated for the treatment of three types of B-cell blood cancers.
   b. The mechanism of action of belinostat is inhibition of phosphatidylinositol 3-kinase (PI3K) delta.
   c. Siltuximab is indicated for the treatment of patients with multicentric Castleman disease.
   d. The mechanism of action of siltuximab is inhibition of leukotrienes.

16. Which of the following statements is correct about droxidopa?
   a. It is metabolized to levodopa, which is its active derivative.
   b. It is a prodrug of norepinephrine, which is responsible for its pharmacological effects.
   c. Most patients experience gastrointestinal adverse events.
   d. It has a long duration of action and is administered once a day.

17. Which of the following statements is correct about pirfenidone?
   a. It is classified as an interleukin-6 inhibitor.
   b. Patients should avoid excessive exposure to sunlight to reduce the risk of photosensitivity reactions.
   c. Exposure of the drug in smokers is significantly greater compared with nonsmokers.
   d. It is metabolized primarily via the CYP3A4 pathway.

18. Which of the following statements is correct about nintedanib?
   a. Headache is the adverse event most often experienced with its use.
   b. It is excreted unchanged in the urine.
   c. Liver function tests should be determined on a periodic basis.
   d. CYP3A4 inducers may increase its action, and concurrent use should be avoided.

19. Which of the following statements is correct?
   a. Eliglustat is classified as a glucosylceramide synthase inhibitor.
   b. Eliglustat is indicated for the treatment of patients with mucopolysaccharidosis type IVA.
   c. Elosulfase alfa is administered every 4 weeks.
   d. Myelosuppression is the most important concern with use of eolsulfase alfa.

20. Which of the following statements is correct?
   a. Metreleptin is indicated for the treatment of patients with Morquio A syndrome.
   b. Metreleptin is administered intravenously over a period of 60 minutes.
   c. Leishmaniasis is transmitted to humans via the bites of mosquitoes.
   d. Miltefosine is administered either 2 or 3 times a day depending on the patient’s weight.

CPE information
To obtain 2.0 contact hours (0.2 CEUs) of CPE credit for this activity, you must complete the online Assessment, the Learning Evaluation, and 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 April 1, 2018, 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.

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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.
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