Objective: To provide information on the most important properties of new therapeutic agents marketed in 2015.

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

Data synthesis: This review covers eight new therapeutic agents marketed in the United States in 2015: edoxaban, secukinumab, panobinostat, palbociclib, lenvatinib, dinutuximab, ceftazidime/avibactam, and isavuconazonium sulfate. Indications and information on dosage and administration for these agents are reviewed, as are the most important pharmacokinetic properties, drug interactions, and other precautions. Practical considerations for use of these new agents are also discussed. Whenever possible, properties of the new drugs are compared with those of older agents marketed for the same indications.

Summary: Edoxaban is the third oral factor Xa inhibitor approved with indications for treatment of nonvalvular atrial fibrillation, deep vein thrombosis, and pulmonary embolism. Secukinumab is a first-in-class human interleukin-17A receptor antagonist indicated for moderate to severe plaque psoriasis. Four new antineoplastic agents have been approved, three of which are available in oral dosage form. Panobinostat is a histone deacetylase inhibitor approved for multiple myeloma. Palbociclib is the first cyclin-dependent kinase inhibitor for metastatic breast cancer. Lenvatinib, a receptor tyrosine kinase inhibitor, is approved to treat differentiated thyroid cancer that is resistant to other therapies. Dinutuximab is a chimeric monoclonal antibody indicated for high-risk neuroblastoma in pediatric patients. Two new qualified infectious disease products (QIDPs) have been approved, making them the fifth and sixth FDA-approved QIDPs available. Ceftazidime was approved in combination with avibactam, a new beta-lactamase inhibitor, for the treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis. Isavuconazonium sulfate is a new azole antifungal approved to treat invasive fungal infections.

Pharm Today. 2015;21(9):79–93.
CPE NEW THERAPEUTIC AGENTS MARKETED IN 2015: PART 1

Objective
In the first part of this four-part series on new therapeutic agents marketed in the United States in 2015, eight new therapeutic agents are covered: edoxaban, secukinumab, panobinostat, palbociclib, lenvatinib, dinutuximab, ceftazidime/avibactam, and isavuconazonium sulfate (Table 1).

New cardiology agent: Edoxaban
For decades, warfarin was the primary anticoagulant used for prevention and treatment of blood clots from deep vein thrombosis (DVT), pulmonary embolism (PE), atrial fibrillation (AF or Afib), or systemic embolism. In recent years, the novel oral anticoagulants, which include dabigatran (Pradaxa—Boehringer Ingelheim), rivaroxaban (Xarelto—Janssen), apixaban (Eliquis—Bristol-Myers Squibb), and most recently, edoxaban (Savaysa—Daiichi Sankyo), have provided alternatives to warfarin. Given the number of options now available, it is important to be familiar with their benefits, risks, and differences to aid providers and patients in choosing the right agent.

Edoxaban is the third available selective oral factor Xa inhibitor, joining rivaroxaban and apixaban. Inhibition of factor Xa reduces thrombin generation and thrombus formation (Figure 1). Figure 1 provides an overview of the clotting cascade and where edoxaban inhibits the process. Table 2 describes the mechanism of action in more detail. Currently, edoxaban has three FDA-approved indications: to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and for the treatment of DVT as well as PE following 5 to 10 days of initial therapy with a parenteral anticoagulant.1

According to the American Heart Association, an estimated 2.7 million Americans are living with AF, the most common cardiac arrhythmia. Untreated AF doubles the risk of heart-related deaths and causes a fourfold to fivefold increased risk for stroke related to a reduction in cardiac output and to atrial and atrial appendage thrombus formation.2

Preassessment questions
Before participating in this activity, test your knowledge by answering the following questions. These questions will also be part of the CPE assessment.
1. Which of the following agents is an interleukin-17A antagonist indicated for moderate to severe plaque psoriasis?
   a. Edoxaban
   b. Secukinumab
   c. Lenvatinib
   d. Isavuconazonium sulfate
2. Which of the following is administered intravenously?
   a. Panobinostat
   b. Palbociclib
   c. Dinutuximab
   d. Secukinumab
3. Which of the following statements is correct about isavuconazonium sulfate?
   a. It is a prodrug of itraconazole.
   b. It is approved to treat Candida species.
   c. It is available only in an I.V. dosage form.
   d. It is indicated for invasive aspergillosis.

Figure 1. Mechanism of action for new oral anticoagulants

Source: Adapted with permission from the American Heart Association.
Venous thromboembolism (VTE) is a major health care problem resulting in significant morbidity and mortality. DVT and acute PE are two manifestations of VTE. The exact number of those affected by DVT and PE is unknown. As many as 900,000 people could be affected annually in the United States, and estimates suggest that 100,000 Americans die of PE each year. One-third of those diagnosed with DVT or PE will have a recurrence within 10 years. Among those

| Table 1. New therapeutic agents marketed in 2015: Part 1 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Generic name** | **Trade name** | **Manufacturer** | **Indication** | **Route** | **Pronunciation** | **FDA approval** |
| **Cardiology** | **Edoxaban** | **Savaysa** | **Daiichi Sankyo** | Treatment of NVAF, DVT, and PE | Oral | e DOX e ban | 1/15 |
| **Dermatology** | **Secukinumab** | **Cosentyx** | **Novartis** | Moderate to severe plaque psoriasis | SubQ | sek ue KIN ue mab | 1/15 |
| **Hematology/oncology** | **Panobinostat** | **Farydak** | **Novartis** | Multiple myeloma | Oral | pan oh BIN oh stat | 2/15 |
| | **Palbociclib** | **Ibrance** | **Pfizer** | Metastatic breast cancer | Oral | pal boe SYE kilb | 2/15 |
| | **Lenvatinib** | **Lenvima** | **Eisai** | Thyroid cancer | Oral | len VA ti nib | 2/15 |
| | **Dinutuximab** | **Unituxin** | **United Therapeutics** | High-risk neuroblastoma | I.V. | Din ue TUX i mab | 3/15 |
| **Infectious disease** | **Ceftazidime/avibactam** | **Avycaz** | **Forest** | cIAI, cUTI, and pyelonephritis | I.V. | SEF tay zi deem/ a vi BAK tam | 2/15 |
| | **Isavuconazonium sulfate** | **Cresemb** | **Astellas** | Treatment of invasive aspergillosis and mucormycosis in adults | Oral, I.V. | eye sa vue koe na ZOE nee um sul FATE | 3/15 |

Abbreviations used: NVAF, nonvalvular atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism; SubQ, subcutaneous; I.V., intravenous; cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections.

| Table 2. Mechanism of action of new therapeutic drugs |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| **Generic name** | **Trade name** | **Mechanism of action** | **Selective factor Xa inhibitor; inhibits free factor Xa and prothrombinase activity and inhibits thrombin-induced platelet aggregation. Inhibitor of factor Xa in the coagulation cascade reduces thrombin generation and thrombus formation.** | **Secukinumab** | **Cosentyx** | Selectively binds to the IL-17A cytokine and inhibits its interaction with the IL-17 receptor. | **Palbociclib** | **Ibrance** | Multitargeted RTK inhibitor of VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4); FGFR1, 2, 3, and 4; and PDGFR-alpha, as well as other tyrosine kinase receptors. Inhibition of these RTKs leads to decreased tumor growth and slowing of cancer progression. | **Lenvatinib** | **Lenvima** | Binds to gD2, which is highly expressed in neuroblastoma, most melanomas, and other tumors. By binding to gD2, dinutuximab induces cell lysis (of gD2-expressing cells) through ADCC and CDC. | **Ceftazidime/avibactam** | **Avycaz** | Inhibits bacterial cell wall synthesis by binding to one or more of the PBPs, which in turn inhibits the final transpeptidation step of the peptidoglycan synthesis in bacterial cell walls, thus inhibiting cell wall biosynthesis; avibactam inactivates some beta-lactamases and protects ceftazidime from degradation. | **Isavuconazonium sulfate** | **Cresemb** | Prodrug inhibits synthesis of ergosterol, which leads to a weakened cell membrane. | **Abbreviations used:** IL-17A, interleukin-17A; HDAC, histone deacetylase; CDK, cyclin-dependent kinase; RTK, receptor tyrosine kinase; VEGFR, vascular endothelial growth factor receptor; FLT, FMS-like tyrosine kinase; KDR, kinase insert domain receptor; FGFR, fibroblast growth factor receptor; PDGFR-alpha, platelet-derived growth factor receptor–alpha; gD2, disialoganglioside; ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; PBPs, penicillin-binding proteins. | **Sources:** References 1, 6, 11, 15, 16, 18, 22, 27. |
who have had a DVT, approximately 50% will have postthrombotic syndrome, which has long-term complications that include pain, swelling, discoloration, and scaling in the affected limb.3

Edoxaban, available as an oral tablet in strengths of 15 mg, 30 mg, and 60 mg, is dosed once daily (see Table 3 for detailed dosing). Peak concentrations are obtained 1–2 hours after dosing, and steady state is achieved in 3 days.1

FDA approval was based on two large pivotal trials: ENGAGE-AF TIMI 48 and Hokusai-VTE.4,5 Patients with NVAF were randomized to edoxaban 30 mg, edoxaban 60 mg, or warfarin. Edoxaban 60 mg was found to be noninferior to warfarin for the primary endpoint of stroke or systemic embolism. The 30-mg treatment arm was less effective than warfarin for the same endpoint as well as the reduction in rate of ischemic stroke.

The Hokusai-VTE study randomized patients with a DVT or PE to either warfarin or edoxaban. All patients received open-label enoxaparin or unfractionated heparin for at least 5 days. The study demonstrated comparable symptomatic events between edoxaban and warfarin.4

Edoxaban is contraindicated in active bleeding, and use is not recommended in patients with mechanical heart valves or with moderate to severe mitral stenosis. Because serious and potential fatal bleeding may occur, patients should be monitored for signs and symptoms of bleeding. In patients with NVAF, bleeding and anemia are the most common adverse drug reactions (ADRs), occurring in more than 5% of patients. The most common ADRs (>1%) seen in patients with DVT or PE include bleeding, rash,

### Table 3. Dosing of new therapeutic agents

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Dosage form</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edoxaban</td>
<td>Savaysa</td>
<td>15-, 30-, and 60-mg oral tablets</td>
<td>DVT and PE: 60 mg once daily after 5–10 days of initial therapy with a parenteral anticoagulant</td>
<td>Prior to initiation, assess CrCL. Do not use in patients with NVAF if CrCL is &gt;95 mL/min.</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>Cosentyx</td>
<td>150-mg SubQ injection</td>
<td>300-mg SubQ once weekly (given as two 150-mg SubQ injections) at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks</td>
<td>Some patients may require only 150 mg per dose. Allow drug to reach room temperature prior to injection.</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Farydak</td>
<td>10-, 15-, and 20-mg oral capsules</td>
<td>20 mg once every other day for three doses each week (on days 1, 3, 5, 8, 10, and 12) during weeks 1 and 2 of a 21-day cycle for up to 8 cycles</td>
<td>May repeat an additional eight cycles (in combination with bortezomib and dexamethasone) in patients experiencing clinical benefit and acceptable toxicity.</td>
</tr>
<tr>
<td>Palbociclib</td>
<td>Ibrance</td>
<td>75-, 100-, and 125-mg oral capsules</td>
<td>125 mg once daily for 21 days, followed by a 7-day rest period to complete a 28-day treatment cycle (in combination with continuous letrozole)</td>
<td>Avoid concomitant use with strong CYP3A4 inhibitors or with moderate or strong CYP3A4 inducers.</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>Lenvima</td>
<td>4- and 10-mg oral capsules</td>
<td>24 mg once daily until disease progression or unacceptable toxicity</td>
<td>Do not take a missed dose within 12 hours of the next dose.</td>
</tr>
<tr>
<td>Dinutuximab</td>
<td>Unituxin</td>
<td>17.5 mg/5 ml single-use vial; I.V.</td>
<td>17.5 mg/m2/d as a diluted I.V. infusion over 10–20 hours for 4 consecutive days for a maximum of five cycles</td>
<td>Give in combination with GM-CSF, IL-2, and isotretinoin.</td>
</tr>
<tr>
<td>Ceftazidime/ avibactam</td>
<td>Avycaz</td>
<td>I.V.</td>
<td>Loading dose: 372 mg (= 200 mg) every 8 hours for six doses (48 hours) via oral (two capsules) or I.V. (one reconstituted vial)</td>
<td>Give in combination with metronidazole for cIAIs.</td>
</tr>
<tr>
<td>Isavuconazo- nium sulfate</td>
<td>Cressemba</td>
<td>I.V., 372 mg</td>
<td>Maintenance dose: 372 mg (= 200 mg) daily via oral (two capsules) or I.V. (one reconstituted vial) starting 12–24 hours after the last loading dose</td>
<td>Infuse over 1 hour; must administer via an infusion set with an inline filter. Do not administer as I.V. bolus.</td>
</tr>
</tbody>
</table>

Abbreviations used: DVT, deep vein thrombosis; PE, pulmonary embolism; NVAF, nonvalvular atrial fibrillation; CrCL, creatinine clearance; SubQ, subcutaneous; CYP, cytochrome P450; I.V., intravenous; GM–CSF, granulocyte-macrophage colony-stimulating factor; IL-2, interleukin-2; cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections.
anemia, and abnormal liver function tests. Edoxaban should not be used by women who are breastfeeding and is not recommended for patients with moderate or severe hepatic impairment. An assessment of renal function is recommended before initiating therapy, and the dose should be reduced to 30 mg per day in patients with renal impairment (creatinine clearance \(\text{CrCL} = 15–50\, \text{mL/min}\)). Edoxaban is metabolized in the liver and is primarily eliminated unchanged in the urine.

There are several important drug interactions to remember. Edoxaban is a substrate of P-glycoprotein. Administering edoxaban concomitantly with other anticoagulants, antiplatelets, and thrombolytics may increase the risk of bleeding. Routine monitoring of coagulation tests is not required; however, edoxaban prolongs the prothrombin and activated prothrombin times.

Key black box warnings include reduced efficacy in NV AF patients with a CrCL greater than 95 mL/min, increased risk of ischemic events with premature discontinuation, and spinal/epidural hematoma in patients receiving neuraxial anesthesia or undergoing spinal puncture. Edoxaban is a Pregnancy Category C drug that should not be used during pregnancy unless the potential benefits outweigh the potential risks to the fetus.

No head-to-head studies have been conducted on edoxaban and the other novel oral anticoagulants dabigatran, rivaroxaban, or apixaban. It is important to note that indications vary among the anticoagulants (Table 4).

**New dermatology agent: Secukinumab**

Psoriasis is a chronic autoimmune disease of the skin characterized by sharply defined erythematous plaques with an overlying silvery scale. Many forms of psoriasis occur, but plaque psoriasis is the most common type. The scalp, extensor elbows, knees, and back are common locations for plaque psoriasis, a disorder that affects women and men equally. Psoriasis may begin at any age, although a bimodal age distribution is seen, as peak times for disease onset are ages 30–39 years and 50–69 years. Genetic factors play an important role in susceptibility to psoriasis.

Secukinumab (Cosentyx—Novartis), a first-in-class human interleukin-17A (IL-17A) receptor antagonist, is indicated for moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Secukinumab is a human IgG1 immunoglobulin monoclonal antibody that selectively binds to the IL-17A cytokine and inhibits its interaction with the IL-17A receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Secukinumab inhibits the release of proinflammatory cytokines and chemokines.

The recommended dose is 300 mg (given as two 150-mg injections) by subcutaneous injection at weeks 0, 1, 2, 3, and 4, followed by 300 mg every 4 weeks. In clinical trials, body weight was found to be a significant variable in secukinumab exposure and clearance. Higher secukinumab exposure was associated with an increased treatment response, and higher body weight (≥90 kg) was associated with a decreased treatment response. For this reason, a 150-mg dose may be acceptable for some patients.

The primary efficacy measure for plaque psoriasis is the Psoriasis Area and Severity Index (PASI) 75 score, which measures a reduction of symptoms by 75% from baseline. When secukinumab was compared with placebo, 72%–82% of patients achieved a PASI 75 score with secukinumab compared with placebo (4.5%). In a head-to-head study between secukinumab and etanercept, PASI 75 scores were 67%–77% and 44%, respectively.

The most common adverse reactions, occurring in more than 1% of patients, were nasopharyngitis (11%–12%), diarrhea (3%–4%), and upper respiratory tract infection (3%). A higher rate of infections (29%–48%) observed in clinical trials appeared to be dose dependent. It is important to note

| Table 4. Anticoagulants and FDA-approved indications |
|-------------------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| **Indication**                | **Warfarin** | **Dabigatran** | **Rivaroxaban** | **Apixaban** | **Edoxaban** | **Enoxaparin** |
| Stroke prevention associated with AF | X | X | X | X | X | – |
| Stroke prevention associated with cardiac valve replacement | X | – | – | – | – | – |
| VTE prophylaxis hip and knee | X | – | X | X | – | X |
| VTE treatment (DVT/PE) | X | X* | X | X | X* | X |
| Decreased risk of recurrent PE/DVT | X | X | X | X | – | – |
| Decreased risk of death/recurrent MI/stroke or SE after MI | X | – | – | – | – | – |

Abbreviations used: AF, atrial fibrillation; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; MI, myocardial infarction; SE, systemic embolism.

*Given after 5–10 days of initial therapy with a parenteral anticoagulant (for ST segment elevation MI and PE inpatients only).
that live vaccines should not be given to patients taking secukinumab. No dosage adjustments are required in renal or hepatic impairment.

There are many drug interactions to consider with secukinumab. Concomitant use with live vaccines, Bacillus Calmette–Guérin (BCG) vaccine, belimumab (Benlysta—GlaxoSmithKline), natalizumab (Tysabri—Biogen), topical tacrolimus, pimecrolimus (Elidel—Valeant), and tofacitinib should be avoided. Secukinumab is Pregnancy Category B, although other agents are currently preferred in pregnant women (Table 5).

While secukinumab is the only IL-17A antagonist currently available, many other agents have the same indication, including etanercept (Enbrel—Amgen), adalimumab (Humira—AbbVie), infliximab, and ustekinumab (Stelara—Janssen).

**New hematology/oncology agents**

The National Cancer Institute (NCI) has estimated that the lifetime risk of developing cancer is approximately 39.6%, with 1.65 million new cases expected to occur in 2015. In 2014, FDA approved 41 new drugs, 9 of which were for the treatment of cancer or a cancer-related condition. In just the first half of 2015, seven new drugs for the treatment of cancer or a cancer-related condition were approved, including the first biosimilar product. Four new oncologic agents are included in this review.

### Panobinostat

Panobinostat (Farydak—Novartis) is an oral antineoplastic approved to treat multiple myeloma in patients who have received at least two prior regimens, including bortezomib (Velcade—Millenium Pharms) and an immunomodulatory agent. Panobinostat must be used in combination with bortezomib and dexamethasone. This new agent works by inhibiting the enzyme histone deacetylase (HDAC). Inhibition of HDAC results in accumulation of acetylated histones and other proteins, an outcome that in turn induces cell cycle arrest and/or apoptosis.

In cancer diagnoses, multiple myeloma is relatively uncommon. The lifetime risk of having multiple myeloma is 1 in 143 (0.7%). According to the American Cancer Society, about 26,850 new cases of multiple myeloma will be diagnosed in the United States in 2015, with approximately 11,000 deaths. Multiple myeloma is more common in men than in women.

Table 3 provides the detailed dosing regimen for panobinostat. Drug interactions are numerous, and coadministration with cytochrome P450 (CYP) 2D6 substrates (e.g., atomoxetine [Strattera—Eli Lilly], metoprolol, and venlafaxine) and strong CYP3A inducers should be avoided. The dose of panobinostat should be reduced when given with strong CYP3A inhibitors. There is no dosage adjustment in patients with renal impairment. Patients with hepatic im-

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Pregnancy category</th>
<th>Comments</th>
<th>Lactation</th>
</tr>
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<tbody>
<tr>
<td>Edoxaban</td>
<td>Category C</td>
<td>Adverse events were observed in animal studies.</td>
<td>Not recommended; unknown if excreted in human milk</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>Category B</td>
<td>Adverse events were observed in animal studies.</td>
<td>Caution; unknown if excreted in human milk</td>
</tr>
<tr>
<td>Panobinostat</td>
<td></td>
<td>Adverse events were observed in animal studies.</td>
<td>Not recommended; unknown if excreted in human milk</td>
</tr>
<tr>
<td>Palbociclib</td>
<td></td>
<td>Adverse events were observed in animal studies.</td>
<td>Not recommended; unknown if excreted in human milk</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td></td>
<td>May cause fetal harm. Adverse events were observed in animal studies.</td>
<td>Not recommended/avoid; unknown if excreted in human milk</td>
</tr>
<tr>
<td>Dinutuximab</td>
<td></td>
<td>May cause fetal harm. No reproductive studies completed. Women should use effective contraception during and for 2 months after treatment.</td>
<td>Not recommended; unknown if excreted in human milk. Potential for serious adverse drug reactions in breastfeeding infants.</td>
</tr>
<tr>
<td>Ceftazidime/avibactam</td>
<td>Category B</td>
<td>Adverse events were not observed in animal studies with ceftazidime but were observed in animal studies with avibactam.</td>
<td>Caution, unknown if avibactam is excreted in human milk. Ceftazidime is excreted in human milk.</td>
</tr>
<tr>
<td>Isavuconazonium sulfate</td>
<td>Category C</td>
<td>Adverse events were observed in animal studies.</td>
<td>Not recommended; unknown if excreted in human milk</td>
</tr>
</tbody>
</table>
Panobinostat is metabolized in the liver and eliminated in the feces and urine.

Almost one-half (48%) of the patients received two or three prior lines of therapy, and more than one-half (57%) had prior stem cell transplantation. The median PFS was 12 months (10.3, 12.9) in the panobinostat arm and 8.1 months (7.6, 9.2) in the placebo arm. Overall survival was not statistically different between groups in the interim analysis. Approval of panobinostat was based on a subgroup analysis of 193 patients who had received prior treatment with both bortezomib and an immunomodulatory agent and had a median of two prior therapies. This is why a specific indication exists for patients who have experienced treatment failure with multiple therapies, since the benefit was greatest in this population. PFS was almost twice as long (10.6 mo vs. 5.8 mo) in the panobinostat-treated patients who had received more than two prior lines of therapy.11,13

Panobinostat has no contraindications; however, black box warnings include severe and fatal cardiac ischemic events, severe arrhythmias, and electrocardiogram (ECG) changes. Arrhythmias may be exacerbated by electrolyte abnormalities. Patients should have an ECG and electrolytes at baseline and periodically. Those who experience diarrhea, nausea, or vomiting may require treatment interruption or dose reduction. Because severe diarrhea occurred in 25% of panobinostat-treated patients, patients should be monitored for symptoms. If symptoms occur, they should start an antibiotic regimen, interrupt the panobinostat until symptoms clear, and then reduce the dose or discontinue panobinostat. In addition, consider administering prophylactic antiemetics as clinically appropriate.

Other warnings include the risk of fatal and serious gastrointestinal and pulmonary hemorrhage, hepatotoxicity, and embryo–fetal toxicity. Patients should have platelets monitored prior to start of therapy and then weekly or more frequently if clinically appropriate. Liver function should be monitored at baseline and regularly during treatment. Women should be advised of the risk to the fetus and to avoid pregnancy. See Table 5 for additional details on pregnancy and lactation.

While other HDAC inhibitors exist (e.g., belinostat, vorinostat), none are currently indicated for multiple myeloma.

Palbociclib
Palbociclib (Ibrance—Pfizer) is a new agent for metastatic breast cancer in postmenopausal women. More specifically, it is for metastatic breast cancer that is human epidermal growth factor receptor 2 (HER2)–negative and estrogen receptor (ER)–positive. Palbociclib was approved for use in combination with letrozole.

Breast cancer in women is the second most common type of cancer in the United States. It forms in the breast tissue and, in advanced cases, spreads to surrounding normal tissue. NCI estimates that 231,840 American women will be diagnosed with breast cancer and 40,290 will die from the disease in 2015. Approximately 12.3% of women will be diagnosed with breast cancer at some point during their lifetime.10

Palbociclib inhibits molecules known as cyclin-dependent kinases 4 and 6, which are involved in promoting cancer cell growth. Palbociclib is one of many new cancer drugs available in an oral dosage form. The recommended starting dose is 125 mg taken once daily with food for 21 days followed by 7 days of no treatment (Table 3).

Approval of palbociclib was based on a study in which patients were randomized to receive palbociclib plus letrozole or letrozole alone. Participants were postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous systemic treatment for their advanced disease. In addition, participants were stratified by site of disease (visceral vs. bone only vs. other) and by how long they had been free of disease. Patients received study treatment until progressive disease, unmanageable toxicity, or consent withdrawal.14

The primary efficacy measure was investigator-assessed PFS. Overall response rate in patients with measurable disease was higher in the palbociclib plus letrozole arm compared with the letrozole-only arm (55.4% vs. 39.4%). Data on overall survival are still pending.14,15

Palbociclib has no contraindications. Three important warnings and precautions exist, however: neutropenia, infections, and fetal harm may occur. Patients should have their complete blood count monitored before initiation of therapy, at the beginning of each cycle, on day 14 of the first two cycles, and as needed. Monitor closely for signs and symptoms of infections, and advise patients of the potential risk to a fetus and to use effective contraception.

The most common adverse effects, seen in more than 10% of patients, were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis.

Palbociclib is metabolized in the liver and eliminated primarily as metabolites in feces. Use of palbociclib with strong CYP3A inhibitors and moderate and strong CYP3A inducers should be avoided. If the strong CYP3A inhibitor cannot be avoided, reduce the palbociclib dose.

Use in pregnancy should be avoided because of the risk of...
fetal harm, and no data exist on use during lactation. Women should use effective contraception to avoid pregnancy. Male fertility may be compromised, based on findings in animals (Table 5). No dose adjustments are necessary in renal or hepatic impairment.\textsuperscript{15}

\textbf{Lenvatinib}

Lenvatinib (Lenvima—Eisai) is newly approved for the treatment of progressive, differentiated thyroid cancer (DTC). Specifically, lenvatinib is for patients whose disease has progressed despite receiving radioactive iodine therapy.\textsuperscript{16}

The most common type of thyroid cancer, DTC is a cancerous growth of the thyroid gland. NCI estimates that 62,450 Americans will be diagnosed with thyroid cancer and 1,950 will die from the disease in 2015.\textsuperscript{10}

Lenvatinib is a receptor tyrosine kinase (RTK) inhibitor, which works by blocking certain proteins from helping cancer cells grow and divide. Similar to panobinostat and palbociclib, lenvatinib is available as an oral daily capsule in two strengths: 4-mg and 10-mg capsules (see Table 3 for detailed dosing). The dose should be reduced in severe renal or hepatic impairment.\textsuperscript{16}

Approval of lenvatinib was based on a trial of 392 patients with locally recurrent or metastatic thyroid cancer that was refractory to radioactive iodine. Patients were randomized 2:1 to receive either lenvatinib 24 mg once daily or placebo until disease progression. The primary outcome measure was PFS. A statistically significant increase in PFS was seen in the lenvatinib-treated arm (median PFS, 18.3 mo) compared with those receiving placebo (median PFS, 3.6 mo).\textsuperscript{17}

Warnings and precautions include hypertension, cardiac failure, arterial thrombotic events, hepatotoxicity, and proteinuria. Adverse reactions that occurred in lenvatinib-treated patients at an incidence of 30% or greater were hypertension, fatigue, diarrhea, arthralgia/myalgia, a decrease in appetite and weight, nausea, stomatitis, headache, vomiting, proteinuria, palmar-plantar erythrodysesthesia syndrome, abdominal pain, and dysphonia.\textsuperscript{16}

There are no contraindications or important drug interactions to note with lenvatinib. Based on its mechanism of action and data from animal models, lenvatinib may cause fetal harm. Advise patients about this risk, as well as the risk of breastfeeding. Advise women to discontinue breastfeeding during treatment (Table 5).\textsuperscript{16}

\textbf{Dinutuximab}

Dinutuximab (Unituxin—United Therapeutics) is a glycolipid disialoganglioside (gD2)-binding monoclonal antibody indicated for high-risk neuroblastoma in combination with granulocyte-macrophage colony stimulating factor (GM–CSF; sargramostim), interleukin-2 (IL-2; aldesleukin) and 13-cis-retinoic acid (RA; isotretinoin) in pediatric patients who achieve at least a partial response to prior first-line multiagent, multimodality therapy.\textsuperscript{18}

Dinutuximab is the first therapy aimed specifically for the treatment of patients with high-risk neuroblastoma. Dinutuximab is an antibody that binds to the gD2 on the surface of neuroblastoma cells.\textsuperscript{18} Neuroblastoma, a rare cancer that forms from immature nerve cells, typically occurs in children younger than 5 years of age. Approximately 1 out of 100,000 children will be diagnosed with neuroblastoma. Patients with high-risk disease have a 40%–50% chance of long-term survival despite aggressive therapy.\textsuperscript{19}

Efficacy of dinutuximab was evaluated in patients with high-risk neuroblastoma who had responded previously to induction therapy and stem-cell transplantation. Patients were randomly assigned to receive standard therapy (six cycles of isotretinoin) or immunotherapy (six cycles of isotretinoin and five concomitant cycles of dinutuximab in combination with alternating GM-CSF and IL-2). The primary endpoints were event-free survival and overall survival. The median duration of follow-up was 2.1 years. Immunotherapy was superior to standard therapy in rates of 2-year, event-free survival (66% for dinutuximab vs. 46% for standard therapy) and 2-year overall survival (86% vs. 75%). Immunotherapy with dinutuximab, GM-CSF, and IL-2 was associated with a significantly improved outcome compared with standard therapy in patients with high-risk neuroblastoma.\textsuperscript{20,21}

Dinutuximab has a complex dosing regimen based on body surface area (Table 3). Although the metabolism and elimination of dinutuximab are unknown, its 10-day half-life warrants appropriate monitoring for adverse effects. The most common adverse reactions (>25%) with dinutuximab are pain, pyrexia, blood dyscrasias, infusion reactions, hypotension, vomiting, diarrhea, capillary leak syndrome, and urticaria. The drug carries the following warnings and precautions, with full details in the product label:\textsuperscript{18}

- Capillary leak syndrome and hypotension
- Infection
- Neurological disorders of the eye
- Bone-marrow suppression
- Electrolyte abnormalities
- Atypical hemolytic uremic syndrome
- Embryo–fetal toxicity

Black box warnings for dinutuximab include serious and potentially life-threatening infusion reactions and neuropathy. Infusion reactions occurred in 26% of patients. Standard infusion protocols should include prehydration and premedication, interruption for severe reactions, and permanent discontinuation should anaphylaxis occur. Dinutuximab should not be administered to any patient with a history of anaphylaxis with previous use.\textsuperscript{18}

Severe neuropathic pain occurs in the majority of patients who use dinutuximab. Grade 3 peripheral sensory neuropathy occurred in 2%–9% of patients. An IV, opioid should be administered before, during, and for 2 hours after completion of the infusion.\textsuperscript{18}
**New infectious disease agents**

The Infectious Diseases Society of America (IDSA) posed a challenge to industry and policymakers to develop and approve 10 new antibiotics by 2020. With the six qualified infectious disease products (QIDPs) FDA approved in the last 2 years, IDSA will likely meet and exceed its goal. QIDP agents were defined under the Generating Antibiotic Incentives Now (GAIN) Act, which was signed into law in July 2012. GAIN encourages development of new antibiotics for neglected diseases. The designation provides an expedited review process and an additional 5 years of marketing exclusivity for antibacterial and antifungal drugs intended to treat serious or life-threatening infections.

**Ceftazidime/avibactam**

Ceftazidime/avibactam (Avycaz—Forest Laboratories) is a combination of a previously approved cephalosporin and avibactam, a new beta-lactamase inhibitor.22 It is the fifth approved antibacterial or antifungal drug product designated as a QIDP. Other FDA-approved QIDP antibiotics, listed in Table 6, include dalbavancin (Dalvance—Durata), tedizolid (Sivextro—Cubist), oritavancin (Orbactiv—The Medicines Company), and ceftolozane/tazobactam (Zerbaxa—Cubist).

Ceftazidime/avibactam is indicated for the treatment of patients aged 18 years or older with the following infections:

- Complicated intra-abdominal infections (cIAI), used in combination with metronidazole
- Complicated urinary tract infections (cUTI), including pyelonephritis

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ceftazidime/avibactam and other antibacterial drugs, the combination should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. In addition, it should be reserved for use in patients who have limited or no alternative treatment options.22

Ceftazidime is a cephalosporin with activity against gram-negative and gram-positive bacteria. The bactericidal action of ceftazidime is mediated through binding to essential penicillin-binding proteins (PBPs). Avibactam is a non-beta-lactam beta-lactamase inhibitor that inactivates some beta-lactamases and protects ceftazidime from degradation by certain beta-lactamases. To date, no cross-resistance with other classes of antimicrobials has been identified. Some isolates resistant to other cephalosporins (including ceftazidime) and to carbapenems may be susceptible to the combination. Table 7 describes the clinical coverage of ceftazidime/avibactam in more detail.22

Ceftazidime/avibactam is available as an injection in single-use vials containing 2 g of ceftazidime and 0.5 g of avibactam. See Table 3 for dosing guidance. Both ceftazidime and avibactam are excreted primarily by the kidneys. Dosage adjustment is recommended in patients with moderate and severe renal impairment and end-stage renal disease (CrCL ≤ 50 mL/min).22

Approval of ceftazidime/avibactam relied in part on FDA’s previous finding of ceftazidime’s safety and efficacy. The clinical data submitted to evaluate efficacy included data from two Phase 2 trials, one each in cUTI and cIAI.23 A formal hypothesis was not prespecified in either trial. Safety data on avibactam, including data from patients who received ceftazidime/avibactam, were also assessed. The contribution of the avibactam component was primarily assessed in in vitro studies and in animal models of infection, where the addition of avibactam restored the activity of ceftazidime against bacteria that are nonsusceptible to ceftazidime.23 Unfortunately, published Phase 3 studies are unavailable to date.

In one of the Phase 2 trials, adult patients with cUTIs were randomized 1:1 to ceftazidime/avibactam or imipenem/cilastatin (Primaxin—Merck). The primary objective was to measure microbiologic response. A switch to oral ciprofloxacin was allowed after completion of at least 4 days of therapy. Total duration of therapy was 7–14 days. Nearly two-thirds of the patients had pyelonephritis: 44 (64.7%) in the ceftazidime/avibactam group and 41 (61.2%) in the imipenem/cilastatin group. Most participants were female (75%), and *Escherichia coli* was the most common pathogen identified. The clinical and microbiologic response for the ceftazidime/avibactam arm was consistent with FDA’s expectation.

### Table 6. FDA-approved QDIPs

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Class</th>
<th>Route</th>
<th>FDA approval</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalbavancin</td>
<td>Dalvance</td>
<td>Durata</td>
<td>Glycopeptide</td>
<td>I.V.</td>
<td>5/14</td>
<td>ABSSSI</td>
</tr>
<tr>
<td>Tedizolid phosphate</td>
<td>Sivextro</td>
<td>Cubist</td>
<td>Oxazolidinone</td>
<td>I.V., oral</td>
<td>6/14</td>
<td>ABSSSI</td>
</tr>
<tr>
<td>Oritavancin</td>
<td>Orbactiv</td>
<td>The Medicines Company</td>
<td>Glycopeptide</td>
<td>I.V.</td>
<td>7/14</td>
<td>ABSSSI</td>
</tr>
<tr>
<td>Ceftolozane/tazobactam</td>
<td>Zerbaxa</td>
<td>Cubist</td>
<td>Fifth-generation cephalosporin</td>
<td>I.V.</td>
<td>12/14</td>
<td>cIAI, cUTI</td>
</tr>
<tr>
<td>Ceftazidime/avibactam</td>
<td>Avycaz</td>
<td>Forest</td>
<td>Third-generation cephalosporin</td>
<td>I.V.</td>
<td>1/15</td>
<td>cIAI, cUTI</td>
</tr>
<tr>
<td>Isavuconazonium sulfate</td>
<td>Cressemba</td>
<td>Astellas</td>
<td>Azole antifungal</td>
<td>I.V., oral</td>
<td>3/15</td>
<td>Invasive aspergillosis, mucormycosis</td>
</tr>
</tbody>
</table>

Abbreviations used: QDIPs, qualified infectious disease products; I.V., intravenous; ABSSSI, acute bacterial skin and skin structure infections; cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections.
for efficacy when treating cUTI.\(^23\)\(^24\)

In the second Phase 2 trial, adults with cIAI were random-ized to receive ceftazidime/avibactam plus metronida-zole or meropenem for 5–14 days. Patients were stratified by baseline severity of disease. The primary measure of efficacy was the clinical outcome measured 2 weeks after therapy. The majority of patients were male (75%) and younger than 65 years of age (90%). The site of infection was the appendix in 47% and the stomach/duodenum in 25% of patients. More than one-third of the patients had polymicrobial infections. The most common pathogens identified from intra-abdominal sites were Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, Aerobic gram-negative bacteria, Citrobacter freundii, Citrobacter koseri, Escherichia coli, Pseudomonas aeruginosa, Enterobacter aerogenes, Enterobacter cloacae, Proteus species, and Klebsiella pneumoniae.

<table>
<thead>
<tr>
<th>QIDP</th>
<th>Diagnosis</th>
<th>Clinical coverage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime/avibactam</td>
<td>cUTI, including pyelonephritis</td>
<td>Gram-negative bacteria, Enterobacter cloacae, Klebsiella pneumoniae, Klebsiella oxytoca, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, Aerobic gram-negative bacteria, Citrobacter freundii, Citrobacter koseri, Escherichia coli, Pseudomonas aeruginosa, Enterobacter aerogenes, Enterobacter cloacae, Proteus species, Klebsiella pneumoniae</td>
</tr>
<tr>
<td>Isavuconazonium sulfate</td>
<td>Invasive aspergillosis</td>
<td>Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Mucorales (e.g., Rhizopus oryzae)</td>
</tr>
<tr>
<td></td>
<td>Invasive mucormycosis</td>
<td>Mucormycetes species</td>
</tr>
</tbody>
</table>

Abbreviations used: QIDP, qualified infectious disease products; cIAI, complicated intra-abdominal infections; cUTI, complicated urinary tract infections. Sources: References 22, 27.

Isavuconazonium sulfate (Cresemba—Astellas) is a new azole antifungal recently approved for treatment of invasive aspergillosis and invasive mucormycosis. It is the sixth approved antibacterial or antifungal drug product designated as a QIDP.\(^27\)

Isavuconazonium sulfate is a water-soluble prodrug of isavuconazole. Isavuconazole, the active form of the drug, inhibits the synthesis of ergosterol, a key component of the fungal cell membrane. Isavuconazole demonstrates fungistatic activity against yeasts similar to the other triazole antifungals (voriconazole and posaconazole) and fungicidal activity against most Aspergillus species. This includes some isolates with resistance to itraconazole, amphotericin B, and caspofungin. In addition, isavuconazole has activity against the Mucorales family, which is key given that until recently, only amphotericin B and posaconazole were the available treatment options. Of note, there is a potential for development of resistance to isavuconazole.\(^28\)

Isavuconazole may be given without regard to meals. After oral administration, the absolute bioavailability of isavuconazole is 98%. It is highly protein bound to albumin (>99%). Isavuconazonium sulfate is available as a lyophilized powder for injection and as an oral capsule. Each capsule contains 186 mg of isavuconazonium sulfate, which is equivalent to 100 mg of isavuconazole. Each single-dose vial for injection contains 372 mg of isavuconazonium sulfate, which
is equivalent to 200 mg of isavuconazole. Whether administered intravenously or orally, loading doses are given every 8 hours for six doses. Conveniently, maintenance doses are given once daily. Additional details about dosing can be found in Table 3.

Efficacy of isavuconazonium in patients with invasive aspergillosis was assessed in the SECURE trial, a Phase 3, randomized, double-blind, active-control, parallel assignment study. Patients with proven or probable invasive fungal disease caused by Aspergillus species or other filamentous fungi were randomized to either isavuconazole or voriconazole for up to 84 days. The primary efficacy measure was all-cause mortality on day 42. Once-daily isavuconazonium (IV. or oral) demonstrated noninferiority to twice-daily voriconazole for the primary endpoint.

Safety and efficacy of isavuconazole were also evaluated in 37 patients with invasive mucormycosis in an open-label noncomparative trial (VITAL). Participants had proven or probable mucormycosis according to pre-established criteria. Rhizopus oryzae and mucormycetes were the most common pathogens identified. All-cause mortality through day 42 and overall response were assessed. While isavuconazole was effective in the treatment of mucormycosis, it has not been evaluated in concurrent, controlled clinical trials.

Currently, isavuconazonium is not FDA approved for the treatment of candidiasis. A Phase 3 study of patients with candidemia and other invasive Candida infections randomized participants to isavuconazole or caspofungin followed by voriconazole. According to clinicaltrials.gov, the study has been completed, but no results have been published.

Contraindications to isavuconazole include coadministration with strong CYP3A4 inhibitors (e.g., ketoconazole or high-dose ritonavir) or inducers (e.g., rifampin or carbamazepine). Drugs with a narrow therapeutic window that are P-gp substrates (e.g., digoxin) may require a dose adjustment when administered concomitantly with isavuconazonium. Patients with familial short QT syndrome should not receive isavuconazole because the drug has been shown to shorten the QTc interval in a concentration-related manner. Serious hepatic reactions have been reported with isavuconazonium. Liver function should be evaluated before initiation of and periodically during therapy. The most frequent adverse reactions, occurring in more than 10% of patients, include nausea, vomiting, diarrhea, headache, elevated liver function tests, hypokalemia, constipation, dyspnea, cough, peripheral edema, and back pain.

Isavuconazonium is a Pregnancy Category C drug because of risk to the fetus. Women should not breastfeed while taking the drug (Table 5). Safety and efficacy in pediatric patients have not been established. No dose adjustment is necessary in renal impairment or in mild to moderate hepatic impairment. The prodrug is rapidly hydrolyzed in the blood to isavuconazole, which is metabolized in the liver. Given orally, isavuconazonium sulfate is eliminated equally in feces and urine.

In addition to new molecular entities and new therapeutic biologics, FDA has approved many new combinations of previously approved drugs, new formulations, and new indications for currently marketed drugs. Although it is not an exhaustive list, Table 8 provides an overview of some of these products.

References

Table 8. Additional approvals of new agents

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>What's new?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindopril arginine; amlodipine besylate</td>
<td>Prestalia</td>
<td>Symplmed Pharmas</td>
<td>Hypertension</td>
<td>New combination of two generics</td>
</tr>
<tr>
<td>Tiotropium bromide; olodaterol</td>
<td>Stiolto Respimat</td>
<td>Boehringer Ingelheim</td>
<td>COPD</td>
<td>New combination</td>
</tr>
<tr>
<td>Albuterol sulfate</td>
<td>Proair Respliclick</td>
<td>Teva</td>
<td>Asthma</td>
<td>New delivery device</td>
</tr>
<tr>
<td>Hydrocodone bitartrate; pseudoephedrine hydrochloride; guaifenesin</td>
<td>Hycofenix</td>
<td>Mikart</td>
<td>Symptomatic relief of cough, nasal congestion; to loosen mucus associated with common cold</td>
<td>Reformulation</td>
</tr>
<tr>
<td>Hydrocodone bitartrate; guaifenesin</td>
<td>Flowtuss</td>
<td>Mikart</td>
<td>Symptomatic relief of cough and to loosen mucus associated with common cold</td>
<td>Reformulation</td>
</tr>
<tr>
<td>Ivecafarin</td>
<td>Kaldeco</td>
<td>Vertex Pharmas</td>
<td>Cystic fibrosis</td>
<td>New indication for pediatrics to age 6</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Elepsia XR</td>
<td>Sun Pharma</td>
<td>Partial-onset seizures</td>
<td>New extended-release branded generic</td>
</tr>
<tr>
<td>Carbidopa; levodopa</td>
<td>Duopa</td>
<td>AbbVie</td>
<td>Parkinson disease</td>
<td>New extended-release enteral suspension</td>
</tr>
<tr>
<td>Carbidopa; levodopa</td>
<td>Rytary</td>
<td>Impax Labs</td>
<td>Parkinson disease</td>
<td>New extended-release branded generic capsule</td>
</tr>
<tr>
<td>Paliperidone palmitate; Methylphenidate hydrochloride</td>
<td>Invega Trinza</td>
<td>Janssen</td>
<td>Schizophrenia</td>
<td>New dosage form for every 3-month I.M. injection</td>
</tr>
<tr>
<td>Glatiramer acetate</td>
<td>Glatopa</td>
<td>Sandoz</td>
<td>Relapsing–remitting multiple sclerosis</td>
<td>New branded generic for Copaxone 20 mg</td>
</tr>
<tr>
<td>Atazanavir; cobicistat</td>
<td>Evotaz</td>
<td>Bristol-Myers Squibb</td>
<td>HIV</td>
<td>New combination</td>
</tr>
<tr>
<td>Darunavir; cobicistat</td>
<td>Prezcobix</td>
<td>Janssen</td>
<td>HIV</td>
<td>New combination</td>
</tr>
<tr>
<td>Lamivudine; raltegravir</td>
<td>Dutrebis</td>
<td>Merck</td>
<td>HIV</td>
<td>New combination</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>Toujeo</td>
<td>Sanofi</td>
<td>Diabetes</td>
<td>New formulation; U-300 insulin glargine</td>
</tr>
<tr>
<td>Insulin lispro</td>
<td>Humalog</td>
<td>Eli Lilly</td>
<td>Diabetes</td>
<td>New delivery device (Kwikpen)</td>
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<tr>
<td>Ferric pyrophosphate citrate</td>
<td>Triferic</td>
<td>Rockwell Medical</td>
<td>Iron replacement therapy in hemodialysis-dependent patients</td>
<td>New iron salt</td>
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<tr>
<td>Phoxillum</td>
<td>Phoxillum</td>
<td>Baxter</td>
<td>Continuous renal replacement therapy</td>
<td>Reformulation</td>
</tr>
<tr>
<td>Ethinyl estradiol; levonorgestrel</td>
<td>Ashlyna</td>
<td>Glenmark</td>
<td>Contraception</td>
<td>New branded generic</td>
</tr>
<tr>
<td>Ethinyl estradiol; levonorgestrel</td>
<td>Vienna</td>
<td>Sandoz</td>
<td>Contraception</td>
<td>New branded generic</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Xifaxan</td>
<td>Salix</td>
<td>Irritable bowel syndrome—diarrhea predominant</td>
<td>New indication</td>
</tr>
</tbody>
</table>

Abbreviations used: COPD, chronic obstructive pulmonary disease; I.M., intramuscular; XR, extended release; ADHD, attention deficit hyperactivity disorder; HIV, human immunodeficiency virus; ESRD, end-stage renal disease.

20. FDA Center for Drug Evaluation and Research. FDA summary review for dinutuximab. Application no. 125516Orig1s000; March 2015.
23. FDA Center for Drug Evaluation and Research. FDA summary review for ceftazidime-avibactam. Application no. 206494Orig1s000; February 2015.
27. Isavuconazonium [product labeling]. Northbrook, IL: Astellas Pharma; March 2015.
28. FDA Center for Drug Evaluation and Research. FDA summary review for isavuconazonium sulfate. Application no. 207500Orig1s000; March 2015.
CPE assessment

Instructions: This assessment 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 drug: indication pairings is correct?
   a. Secukinumab : high-risk neuroblastoma
   b. Edoxaban : prevention of stroke
   c. Palbociclib : metastatic breast cancer
d. Dinutuximab : plaque psoriasis

2. Which of the following drugs may be administered every 8 hours?
   a. Panobinostat
   b. Ceftazidime/avibactam
c. Dinutuximab
d. Lenvatinib

3. Which of the following statements is correct?
   a. Panobinostat must be used in combination with bortezomib and dexamethasone.
   b. Dinutuximab must be used in combination with letrozole.
c. Palbociclib must be used in combination with sargramostim, interleukin-2, and isotretinoin.
d. Isavuconazonium must be used in combination with metronidazole.

4. With the use of which of the following agents is bleeding the most important risk?
   a. Palbociclib
   b. Panobinostat
c. Dinutuximab
d. Edoxaban

5. Which of the following statements is correct about secukinumab?
   a. Edoxaban is approved for deep vein thrombosis prophylaxis after hip and knee surgery.
   b. Edoxaban is dosed 30 mg twice daily.
c. Edoxaban should not be used in patients with non-valvular atrial fibrillation whose creatinine clearance is greater than 95 mL/min.
d. Edoxaban was superior to warfarin for the prevention of stroke.

6. Which of the following statements is correct about palbociclib?
   a. Efficacy of palbociclib in clinical trials was measured using the Psoriasis Area and Severity Index score.
   b. All patients should receive the 300-mg dose.
c. Dosage adjustments are required in renal impairment.
d. Live vaccines may be administered to patients taking palbociclib.

7. Which of the following statements is correct about panobinostat?
   a. It must be given in combination with letrozole.
   b. It binds to the glycolipid disialoganglioside.
c. Panobinostat may be used in treatment-naive patients.
d. Severe diarrhea occurred in 25% of patients.

8. Which of the following statements is correct about panobinostat?
   a. Panobinostat is indicated for multiple sclerosis.
   b. Women should use effective contraception during and for 1 month after treatment.
c. Panobinostat is a tyrosine kinase inhibitor of facular endothelial growth factor receptors.
d. Panobinostat is dosed 20 mg by mouth daily for 3 weeks.

CPE information

To obtain 2.0 contact hours (0.2 CEUs) of CPE credit for this activity, you must complete the online assessment and 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 assessment. Pharmacists who successfully complete this activity before September 1, 2018, can receive CPE credit. Your statement of credit will be available upon successful completion of the assessment and evaluation and will be stored in your My Training Page and on CPE Monitor for future viewing/printing.

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3. To receive CPE credit, select Enroll Now or Add to Cart from the left navigation and successfully complete the assessment (with randomized questions) and 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.
9. Which of the following statements is correct about palbociclib?
   a. Palbociclib must be used in combination with isotretinoin.
   b. Palbociclib is a tyrosine kinase inhibitor.
   c. Neutropenia, infections, and fetal harm are three significant warnings with palbociclib.
   d. Palbociclib has no significant drug interaction concerns.

10. Which of the following statements is correct about lenvatinib?
    a. It is approved for use as first-line therapy in patients with newly diagnosed thyroid cancer.
    b. No dose adjustment is required in severe renal or hepatic impairment.
    c. Lenvatinib prolonged survival compared with placebo.
    d. The most common adverse reactions with lenvatinib include bleeding, rash, and anemia.

11. Which of the following statements is correct about lenvatinib?
    a. Lenvatinib is a histone deacetylase inhibitor.
    b. Lenvatinib is approved for use in pregnancy.
    c. Lenvatinib is dosed once daily until disease progression or unacceptable toxicity.
    d. Two warnings for lenvatinib include capillary leak syndrome and neurological eye disorders.

12. Which of the following statements is correct about dinutuximab?
    a. Immunotherapy with dinutuximab was noninferior to standard therapy.
    b. Dinutuximab must be given in combination with IL-17.
    c. Dinutuximab is available in an oral dosage form.
    d. Severe neuropathic pain may result from use of dinutuximab.

13. Which of the following statements is correct about dinutuximab?
    a. Dinutuximab is dosed 300 mg subcutaneously once weekly at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks.
    b. An IV. opioid should be administered before, during, and for 2 hours after completion of a dinutuximab infusion.
    c. Dinutuximab is approved for use as first-line therapy in patients with newly diagnosed high-risk neuroblastoma.
    d. Embryo–fetal harm is not a concern with dinutuximab.

14. Which of the following statements is correct about ceftazidime/avibactam?
    a. It is FDA approved to treat pyelonephritis.
    b. It is classified as an extended-spectrum penicillin.
    c. It must be used in combination with meropenem for the treatment of complicated intra-abdominal infections.
    d. It is FDA approved to treat nosocomial pneumonia.

15. Which of the following statements is correct about ceftazidime/avibactam?
    a. It does not need to be dose adjusted in moderate or severe renal impairment.
    b. Ceftazidime/avibactam has activity against Bacteroides fragilis but not Proteus mirabilis.
    c. Ceftazidime will not produce a false-positive reaction for glucose in the urine.
    d. Ceftazidime/avibactam has activity against Pseudomonas aeruginosa.

16. Which of the following drugs would be safest in pregnancy?
    a. Lenvatinib
    b. Secukinumab
    c. Palbociclib
    d. Panobinostat

17. Which of the following statements is correct about isavuconazonium sulfate?
    a. Isavuconazonium sulfate was superior to voriconazole for the treatment of aspergillosis.
    b. It must be separated from meals.
    c. Each capsule contains 100 mg of isavuconazonium sulfate, which is equivalent to 186 mg of isavuconazole.
    d. Liver function should be evaluated before initiation of isavuconazonium sulfate and during therapy.

18. Which of the following statements is correct about isavuconazonium sulfate?
    a. It is a prodrug of itraconazole.
    b. It is approved to treat Candida species.
    c. It is available only in an IV. dosage form.
    d. It is approved to treat Aspergillosis species.

19. Which of the following is administered intravenously?
    a. Panobinostat
    b. Palbociclib
    c. Dinutuximab
    d. Secukinumab

20. Which of the following agents is an interleukin-17A antagonist indicated for moderate to severe plaque psoriasis?
    a. Edoxaban
    b. Secukinumab
    c. Lenvatinib
    d. Isavuconazonium sulfate