Abstract

**Objective:** To provide information regarding the most important properties of the new therapeutic agents marketed in the first half of 2011.

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

**Data synthesis:** 14 new therapeutic agents were marketed in the United States during the first half of 2011, 7 of which were reviewed in part 1 of this two-part series. The other seven new drugs marketed during this time period are considered in this article: boceprevir, telaprevir, roflumilast, abiraterone acetate, ipilimumab, tesamorelin acetate, and spinosad. Indications and information on dosage and administration for these agents are reviewed, as are the most important pharmacokinetic properties, adverse events, drug interactions, and other precautions. Practical considerations for the use of these new agents are also discussed. When possible, the properties of the new drugs are compared with those of older agents marketed for the same indications.

**Conclusion:** The new drugs considered in this article have important properties and/or a mechanism of action that distinguish them from previously marketed drugs. Boceprevir and telaprevir are classified as hepatitis C virus protease inhibitors and inhibit viral replication. When either agent is used in a regimen with peginterferon alfa and ribavirin, a significantly higher percentage of patients experience sustained virologic responses compared with the two-drug regimen of peginterferon alfa and ribavirin that has been the standard of treatment. Roflumilast has a unique mechanism of action and may decrease the number of exacerbations experienced by certain patients with chronic obstructive pulmonary disease. Abiraterone is an androgen biosynthesis inhibitor that reduces the formation of testosterone precursors in multiple tissues and has been demonstrated to prolong survival in patients with castration-resistant prostate cancer. Ipilimumab is the first drug to be approved for the treatment of lipodystrophy and is indicated for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. Spinosad is a pediculicide that is more effective than permethrin in the treatment of head lice infestation. An understanding of the properties of these medications is important for the pharmacist to effectively counsel patients about their use and to serve as a valuable source of information for other health professionals regarding these drugs.

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**Learning objectives**

At the conclusion of this knowledge-based activity, the pharmacist will be able to:

- Identify the new therapeutic agents marketed during January to June 2011 and explain their appropriate use.
- Identify the indications and the most important adverse events and other risks of each of the new therapeutic agents.
- State the route of administration for each new drug and the important considerations regarding dosage and administration.
- Demonstrate appropriate patient counseling regarding the use of the new medications and the precautions to be observed.

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**Accreditation information**

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HCV infection is often experienced in patients who are

Antiviral agents

Hepatitis C virus (HCV) infection is characterized by inflam-
mation of the liver, which can lead to reduced liver function and liver failure. The infection can develop in a number of ways, including exposure to blood that is infected with the virus, being born to a mother with HCV, having a sexual rela-
tionship with an infected person, sharing a needle, sharing personal items such as a razor or toothbrush with someone who is infected, and using unsterilized tattoo or piercing instru-
ments. After the initial infection with HCV, most people develop chronic HCV infection. Many patients with the infec-
tion do not experience symptoms until liver damage occurs, which may take several years. Some develop cirrhosis of the liver, which can lead to liver damage with complications such as bleeding, jaundice, fluid accumulation in the abdo-
men, infections, and/or liver cancer. Liver disease resulting from HCV infection is the most frequent reason for which liver transplants are needed by patients in the United States.

More than 3 million Americans have chronic HCV infec-
tion, with genotype 1 infection being the most common form. The standard of treatment has been a combination regi-
men that includes peginterferon alfa (peginterferon alfa-2a [Pegasys], peginterferon alfa-2b [PegIntron]) plus ribavirin (e.g., Copegus, Rebetol) for a period of 48 weeks. This treat-
ment has produced sustained virologic responses (SVRs), characterized by undetectable plasma HCV RNA 24 weeks following discontinuation of therapy that is considered to be a cure of the infection. However, SVRs are attained in fewer than 50% of patients.

Two new and similar antiviral agents have been ap-
proved and marketed within a short time of each other and represent an important advance in the treatment of chronic HCV infection. Boceprevir (Victrelis—Merck) and telaprevir (Incivek—Vertek) are classified as HCV protease inhibitors and interfere with actions that are necessary for replication of the HCV virus. They act by inhibiting the HCV nonstructur-
al protein NS3/4A serine protease that is necessary for the proteolytic cleavage of the HCV-encoded protein into mature forms of the proteins necessary for viral replication. Because of the large number of similarities in the properties and use of the two new drugs, they are considered together in the first part of this review, then as individual agents.

Boceprevir and telaprevir are administered orally, and their labeled indications are very similar. Boceprevir is indi-
cated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavi-
rin, in adult patients (age ≥18 years) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

The indication for telaprevir is similar but specifically mentions prior null responders, partial responders, and relaps-
ers as among the patients who were previously treated with an interferon-based regimen.

Neither boceprevir nor telaprevir should be used alone, and they should always be used in combination with pegin-
terferon alfa and ribavirin in the treatment of HCV infection. The clinical studies of the regimens including each of the new drugs have demonstrated a much higher percentage of pa-
ients experiencing SVRs (i.e., cures) compared with the peginterferon alfa/ribavirin regimens.

Because boceprevir and telaprevir must be used in con-
junction with peginterferon alfa and ribavirin, the contraindi-
cations, warnings, and other pertinent information regarding these latter two agents must be considered when the three-
drug regimen is being planned and used. Anemia has been re-
ported with peginterferon alfa and ribavirin therapy, and the addition of boceprevir or telaprevir is associated with an additional decrease in hemoglobin concentrations and the oc-
currence of anemia in approximately twice as many patients compared with those receiving peginterferon alfa and ribavi-
rin. Complete blood counts should be closely monitored.

Boceprevir and telaprevir are both classified in Pregnan-
cy Category B. However, because ribavirin may cause birth defects and fetal death, the three-drug regimens including one of the two new drugs are classified in Pregnancy Cat-
egory X and are contraindicated in pregnant women and in men whose female partners are pregnant. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of ther-
apy. Women of childbearing potential and men must use at least two forms of effective contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time. Systemic hormonal contraceptives may not be as effective when boceprevir or telaprevir is being used, and two effective nonhormonal methods of contraception (e.g., barrier methods) should be used.

HCV infection is often experienced in patients who are
coinfected with hepatitis B virus and/or human immunodeficiency virus (HIV). However, the effectiveness and safety of boceprevir and telaprevir have not been established in patients with coinfections. The new drugs also have not been evaluated in patients who have received organ transplants or in pediatric patients.

Boceprevir is a strong inhibitor of cytochrome P450 (CYP)3A4/5 and is partly metabolized by these pathways. It is also a potential inhibitor of P-glycoprotein (P-gp) and is a substrate for this transporter. Telaprevir is an inhibitor of CYP3A and P-gp and a substrate for both. Both drugs are likely to interact with numerous other medications. For example, by inhibiting CYP3A pathways, boceprevir and telaprevir may increase and prolong the therapeutic effect and adverse events of other medications that are metabolized via this pathway. As substrates for CYP3A and P-gp, the action of the new antiviral drugs may be increased by the concurrent use of inhibitors of these pathways and decreased by inducers. Some of these interactions are of sufficient importance that the concomitant use of boceprevir or telaprevir with the interacting agents is contraindicated.

The use of rifampin and St. John’s wort with either boceprevir or telaprevir is contraindicated because of a likely reduction in the activity of the latter agents that may result in a loss of virologic response. The use of carbamazepine, phenobarbital, or phenytoin is contraindicated with boceprevir and telaprevir for which precautions and/or dosage adjustments are necessary in the labeling for the new drugs. The activity of the new antiviral agents may be increased by the concurrent use of clarithromycin and azole antifungal agents (e.g., itraconazole) and decreased by rifabutin, dexamethasone, HIV protease inhibitors, and efavirenz. The use of boceprevir and telaprevir may decrease the activity of ethinyl estradiol (e.g., in hormonal contraceptives) and increase the activity of antiarrhythmic agents (amiodarone, bepridil, flecainide, propafenone, quinidine), digoxin, azole antifungal agents, colchicine, desipramine, trazodone, alprazolam, calcium channel blockers, bosentan, cyclosporine, sirolimus, tacrolimus, and the phosphodiesterase type 5 inhibitors used for erectile dysfunction. In patients treated with boceprevir or telaprevir, it is recommended that the dosage of sildenafil not exceed 25 mg every 48 hours and that the dosage of tadalfil not exceed 10 mg in 72 hours. The labeling for boceprevir notes that the dosage of vardenafil should not exceed 2.5 mg in 24 hours, whereas the labeling for telaprevir states that the dosage of vardenafil should not exceed 2.5 mg in 72 hours. There have been reports of both increased and decreased activity of warfarin when boceprevir or telaprevir is used concurrently, and the international normalized ratio should be closely monitored.

The product labeling should be consulted for more detailed information and recommendations regarding the interactions described above, as well as additional potential interactions.

Boceprevir and telaprevir are discussed on an individual basis in the following discussions.

Table 1. New therapeutic agents marketed in the United States from January to June 2011*

<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>Abiraterone acetate</td>
<td>Zytiga</td>
<td>Janssen</td>
<td>Antineoplastic agent</td>
<td>Oral</td>
<td>1-P</td>
</tr>
<tr>
<td>Boceprevir</td>
<td>Victrelis</td>
<td>Merck</td>
<td>Antiviral agent</td>
<td>Oral</td>
<td>1-P</td>
</tr>
<tr>
<td>Telaprevir</td>
<td>Incivek</td>
<td>Vertex</td>
<td>Antiviral agent</td>
<td>Oral</td>
<td>1-P</td>
</tr>
<tr>
<td>Spinosad</td>
<td>Natroba</td>
<td>ParaPRO</td>
<td>Pediculicide</td>
<td>Topical</td>
<td>1-S</td>
</tr>
<tr>
<td>Tesamorelin acetate</td>
<td>Egrifta</td>
<td>Serono; Thera-technologies</td>
<td>Agent for lipodystrophy in HIV-infected patients</td>
<td>Subcutaneous</td>
<td>1-S</td>
</tr>
</tbody>
</table>

*Additional agents marketed during this time period are considered in part 1 of this two-part series (Pharmacy Today. 2011(Oct);17(10):86–95.)

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

Boceprevir (Victrelis—Merck) was evaluated in studies in which patients were initially treated with peginterferon alfa-2b and ribavirin for a period of 4 weeks, followed by some patients continuing with the two-drug regimen plus placebo for a total of 48 weeks and other patients also receiving boceprevir for 24 to 44 weeks in regimens with peginterferon alfa and ribavirin that continued for up to a total of 48 weeks. In the study in which patients had not been previously treated with antiviral agents, approximately two-thirds of the patients treated with the regimen that included boceprevir experienced an SVR compared with 38% of those treated with the two-drug regimen. Both regimens were less effective in black patients than in nonblack patients.

In another study, boceprevir was evaluated in patients who had failed previous therapy with peginterferon alfa and ribavirin (i.e., patients experienced a decrease in HCV-RNA viral load but did not achieve SVR [partial responders] or had undetectable HCV-RNA at the end of prior treatment with a subsequent detectable HCV-RNA in plasma [relapsers]). Following the initial treatment with peginterferon alfa-2b plus ribavirin for 4 weeks, approximately two-thirds of the patients treated with the three-drug regimen including boceprevir for a total of 48 weeks experienced an SVR compared with 23% of those treated with the two-drug regimen. Patients who experienced less than a 2-log₁₀ decrease in HCV-RNA by week 12 of previous treatment (prior null responders) were not included in the study.

The most frequently reported adverse events (and their incidences in patients receiving the three-drug and two-drug regimens, respectively) in the study in previously untreated patients included anemia (50%, 30%), neutropenia (25%, 19%), nausea (46%, 42%), dysgeusia (35%, 16%), fatigue (38%, 59%), chills (34%, 29%), and insomnia (34%, 34%). Serious adverse events were reported in 11% of patients treated with the three-drug regimen including boceprevir and in 8% of patients treated with the two-drug regimen.

Both anemia and neutropenia have occurred with the use of peginterferon alfa and ribavirin. However, the addition of boceprevir to the regimen is associated with an additional decrease in hemoglobin concentrations and risk of anemia and a worsening of neutropenia. Complete blood counts should be obtained pretreatment and at treatment weeks 4, 8, and 12 and should be monitored closely at other time points, as appropriate. If the hemoglobin concentration is less than 10 g/dL, a decrease in dosage or interruption of ribavirin is recommended, and if hemoglobin is less than 8.5 g/dL, discontinuation of ribavirin is recommended. Decreases in neutrophil counts may require dosage reduction or discontinuation of peginterferon alfa and ribavirin.

Boceprevir should be administered with food because exposure of the drug has been reported to be increased by up to 65% compared with administration in the fasting state. Its bioavailability is similar regardless of meal type (e.g., high versus low fat) or whether taken 5 minutes prior to eating, during a meal, or immediately following completion of the meal. In addition to being metabolized via the CYP3A4/5 pathway, boceprevir also undergoes metabolism through the aldo-ketoreductase-mediated pathway to metabolites that are inactive against HCV. The drug is eliminated primarily by the liver. Dosage adjustment is not necessary in patients with renal impairment and is not recommended in patients with hepatic impairment.

Boceprevir is administered as part of a regimen that also includes peginterferon alfa and ribavirin and must not be used in the absence of these two agents. Treatment is initiated with the latter two agents for the first 4 weeks of therapy.

Boceprevir capsules are supplied in a 200-mg potency, and the drug is administered in a dosage of 800 mg (four capsules) three times daily (every 7–9 hours) with food (meal or light snack). The use of boceprevir is started after 4 weeks of treatment with peginterferon alfa and ribavirin. The duration of treatment is based on a patient’s HCV-RNA concentrations at treatment weeks 8, 12, and 24, using response-guided therapy guidelines. In previously untreated patients without cirrhosis in whom HCV-RNA is undetectable at treatment weeks 8 and 24, the three-drug regimen is continued and completed at treatment week 28. In previous partial responders or relapsers without cirrhosis, and in whom HCV-RNA is undetectable at treatment weeks 8 and 24, the three-drug regimen is continued and completed at treatment week 36. For either previously untreated patients or previous partial responders or relapsers in whom HCV-RNA is detectable at week 8 but undetectable at week 24, the three-drug regimen should be continued and completed through week 36, with peginterferon and ribavirin being continued through week 48.

In patients with compensated cirrhosis, peginterferon alfa and ribavirin should be used for the first 4 weeks, followed by the three-drug regimen including boceprevir for 44 weeks.

If a dose of boceprevir is missed and it is more than 2 hours before the next dose, the missed dose should be taken with food. If a dose is missed and it is less than 2 hours before the next dose, the missed dose should be skipped.

Telaprevir

Telaprevir (Incivek—Vertek) was evaluated in three studies, two of which were in previously untreated patients and the other in previously treated patients including relapsers, partial responders, and null responders. The SVR rate for patients treated with telaprevir as part of a three-drug regimen, across all studies and across all patient groups, was between 20% and 45% higher than in the patients treated with peginterferon alfa and ribavirin. In one of the studies in previously untreated patients, 79% of those treated with telaprevir (for a period of 12 weeks) as part of a three-drug regimen experienced an SVR compared with 46% of those treated with the two-drug regimen plus placebo. Of the patients treated with the three-drug regimen, 48% had undetectable HCV-RNA at weeks 4 and 12 (extended rapid virologic response [eRVR]) compared with 8% of those treated with the two-drug regimen. The patients who experienced eRVR received 24 weeks of peginterferon alfa plus ribavirin treatment, and those who
did not have undetectable HCV-RNA at weeks 4 and 12 (no eVR) received 48 weeks of peginterferon alfa plus ribavirin treatment. Among the eVR patients treated with the three-drug regimen including telaprevir, 92% experienced an SVR.

In a study in previously treated patients, telaprevir or placebo was administered for a period of 12 weeks and peginterferon plus ribavirin for 48 weeks. The SVR rates for the three- and two-drug regimens were 86% and 22% in prior relapsers, 59% and 15% in prior partial responders, and 32% and 5% in prior null responders, respectively. A high proportion of previous null responders (particularly those with cirrhosis) did not achieve an SVR and had telaprevir resistance-associated substitutions emerge on treatment with the new drug.

The most frequently reported adverse events (and their incidences in patients receiving the three- and two-drug regimens, respectively) included rash (56%, 34%), fatigue (56%, 50%), pruritus (47%, 28%), nausea (39%, 28%), anemia (36%, 17%), diarrhea (26%, 17%), vomiting (13%, 8%), hemorrhoids (12%, 3%), anorectal discomfort (11%, 3%), and dysgeusia (10%, 3%). Serious adverse events occurred in 3% of the patients treated with the three-drug regimen including telaprevir compared with none of the patients treated with the two-drug regimen.

Serious skin reactions, including DRESS (drug rash with eosinophilia and systemic symptoms) and Stevens-Johnson syndrome were reported in less than 1% of patients treated with telaprevir. Each of these patients required hospitalization, but all recovered. If a serious skin reaction occurs, telaprevir and the other agents in the regimen should be immediately discontinued. Many patients in the clinical studies experienced a rash, and these patients should be monitored with respect to worsening of the rash or development of systemic symptoms. If a rash worsens and becomes severe, or if systemic symptoms develop, treatment with telaprevir should be discontinued.

The addition of telaprevir to a regimen with peginterferon alfa and ribavirin is associated with an additional decrease in hemoglobin concentrations and risk of anemia. Hemoglobin should be monitored prior to and at least every 4 weeks during telaprevir combination treatment. For the management of anemia, a reduction in the dosage of ribavirin should be considered. If this intervention is not adequate, the discontinuation of telaprevir should be considered.

Approximately 75% of patients experienced elevated uric acid concentrations during the period of treatment with telaprevir. Chemistry evaluations (uric acid, serum creatinine, electrolytes, hepatic enzymes, bilirubin, thyroid-stimulating hormone) and hematology evaluations (including white cell differential count) are recommended at weeks 2, 4, 8, and 12 or as clinically appropriate.

Telaprevir interconverts to an R-diastereoisomer, which is the major metabolite in plasma and is approximately 30-fold less potent than telaprevir. When administered with a standard-fat meal, the exposure to telaprevir was increased by 237% compared with when it was administered under fasting conditions. Therefore, it should always be administered with food (not low fat).

Telaprevir undergoes extensive metabolism in the liver, primarily via the CYP3A4 pathway. Approximately 80% of a dose is eliminated in the feces, 10% in exhaled air, and 1% in urine. Dosage adjustment is not necessary in patients with renal impairment or in patients with mild hepatic impairment. The use of telaprevir is not recommended in patients with moderate or severe hepatic impairment.

Telaprevir is administered as part of a regimen that also includes peginterferon alfa and ribavirin, and it must not be used as monotherapy. Tablets are supplied in a 375-mg potency, and the recommended dosage is 750 mg (two tablets) three times daily (every 7–9 hours) with food (not low fat). Telaprevir, peginterferon alfa, and ribavirin are used as triple therapy for the first 12 weeks of treatment. HCV-RNA concentrations should be monitored at weeks 4 and 12 to determine the effectiveness of treatment and treatment duration. In patients who were not previously treated or had a prior relapse, if HCV-RNA is undetectable at weeks 4 and 12, treatment with peginterferon alfa and ribavirin should be continued for an additional 12 weeks (total of 24 weeks). If HCV-RNA is detectable at weeks 4 and/or 12, and in all patients who are prior partial responders and null responders, treatment with peginterferon alfa and ribavirin should be continued for an additional 36 weeks (total of 48 weeks). Treatment-naïve patients with cirrhosis who have undetectable HCV-RNA at weeks 4 and 12 also may benefit from a total of 48 weeks of treatment.

If a dose of telaprevir is missed and it is less than 4 hours after the time when the dose is usually administered, the patient should take the dose with food as soon as possible. If more than 4 hours have elapsed from the time the dose would usually be administered, the missed dose should be skipped.

Agent for chronic obstructive pulmonary disease
Chronic obstructive pulmonary disease (COPD) is a progressive, irreversible lung disease that is often associated with chronic bronchitis or emphysema and is typically characterized by symptoms such as breathlessness, chronic cough, and excessive production of mucus. A marked worsening of symptoms (i.e., exacerbation) may last for several weeks and be severe enough to require hospitalization. COPD is the fourth leading cause of death in the United States and is most often caused by cigarette smoking.

The medications used most often in the treatment of COPD include bronchodilators (e.g., beta₂-adrenergic receptor agonists [e.g., salmeterol {Serevent}]), anticholinergic agents (e.g., ipratropium [Spiral]), and inhaled corticosteroids (budesonide, fluticasone propionate that are used in combination formulations {Symbicort, Advair} with a beta₂ agonist). The specific agent(s) used depends on the severity of the symptoms and the urgency for treatment.

Roflumilast (Daliresp—Forest) and its active metabolite (roflumilast N-oxide) are selective inhibitors of the enzyme phosphodiesterase 4 (PDE4). PDE4 is a major cyclic-3',5'-adenosine monophosphate (cAMP)-metabolizing enzyme in
lung tissue, and inhibition of this enzyme results in accumulation of intracellular cAMP. Although the specific mechanism of action through which roflumilast provides its therapeutic benefit has not been fully clarified, it is thought to be related to the effects of increased intracellular cAMP in lung cells and a resultant reduction of inflammation.

Roflumilast is specifically indicated as a treatment to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. It has not been evaluated for the treatment of COPD associated with emphysema. The new drug is not a bronchodilator and is not indicated for the relief of acute bronchospasm.

The effectiveness of roflumilast was demonstrated in multiple studies, including two 1-year trials in which more than 1,500 patients were treated with the new drug. The rate of moderate or severe exacerbations in those treated with roflumilast was reduced significantly compared with placebo, with a 15% reduction in exacerbations in one trial and an 18% reduction in the other. The clinical benefit provided has been described by many as “modest,” and an initial question has been posed as to whether the benefit was greater than the risk of systemic adverse events associated with the drug. However, the potential for the drug to provide additional benefit for patients with severe COPD, as well as the limited and specific focus of the indication to be included in the labeling, resulted in the drug’s approval by the Food and Drug Administration (FDA).

The adverse events most frequently experienced in the clinical studies of roflumilast included diarrhea (10%), nausea (5%), headache (4%), back pain (3%), and insomnia (2%). Weight loss was reported in 8% of patients treated with roflumilast compared with 2% of those receiving placebo. In the 1-year studies, 20% of patients treated with the new drug experienced moderate weight loss (defined as between 5% and 10% of body weight) compared with 7% of those who received placebo. Patients treated with roflumilast should have their weight monitored regularly.

Psychiatric adverse events (e.g., insomnia, anxiety, depression) were reported more often (6%) in patients treated with roflumilast than in those receiving placebo (3%). Suicidal ideation and behavior have been reported, and patients, their caregivers, and families should be informed of the importance of being alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts, or other mood changes.

Roflumilast is classified in Pregnancy Category C and should not be used in a pregnant woman unless the anticipated benefit justifies the risk to the fetus. It should not be used during labor or delivery or by women who are nursing. The effectiveness and safety of roflumilast in pediatric patients have not been evaluated.

Following oral administration, the absolute bioavailability of roflumilast is approximately 80%. The drug is converted to its active metabolite primarily via the CYP1A2 and -3A4 pathways. Although the parent drug is three times as potent as its metabolite, the plasma exposure of the metabolite is about 10-fold greater. Roflumilast is not detectable in the urine, and only a trace amount of the active metabolite is present. Dosage adjustment is not necessary in patients with impaired renal function.

The use of roflumilast is contraindicated in patients with moderate to severe hepatic impairment, and caution must be exercised if it is used in patients with mild impairment of hepatic function. The activity of the new drug may be increased by the concurrent use of a CYP3A4 inhibitor (e.g., ketoconazole, erythromycin) or dual CYP3A4/1A2 inhibitors (e.g., fluvoxamine) and decreased by the concurrent use of CYP3A4 inducers (e.g., rifampin, carbamazepine).

The recommended dosage of roflumilast is 500 µg once a day, and it may be administered without regard to food. The drug is supplied in tablets in a 500-µg potency.

**Antineoplastic agents**

**Abiraterone acetate**

The treatment of prostate cancer may include surgery, radiation, and/or medications. Because testosterone stimulates the growth of prostate tumors, the goal of drug therapy is to reduce the production of testosterone and block its effects (i.e., androgen deprivation therapy; medical castration). Medical castration (i.e., hormonal treatment) blocks androgen production in the testes and, at least initially, often provides effective treatment. However, many patients continue to produce androgens in the adrenal glands and prostate tumor and eventually experience castration-resistant (hormone-refractory) prostate cancer.

Until recently, a regimen based on docetaxel (e.g., Taxotere) has been the only treatment that has been demonstrated to prolong survival in men with castration-resistant prostate cancer. However, in a period of little more than a year, three new drugs have been approved for the treatment of metastatic prostate cancer. In 2010, sipuleucel-T (Provenge), an autologous cellular immunotherapy, was approved for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer, and cabazitaxel (Jevtana), a taxane antineoplastic agent, was approved for use in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer previously treated with a docetaxel-containing regimen. Both sipuleucel-T and cabazitaxel are administered intravenously.

In early 2011, abiraterone acetate (Zytiga—Centocor Ortho Biotech) was approved for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who received previous chemotherapy containing docetaxel. Following oral administration, the new drug is converted to abiraterone, its active metabolite, via hydrolysis by esterases. Abiraterone is an androgen biosynthesis inhibitor that inhibits 17 alpha-hydroxylase/C17,20-lyase (CYP17), an enzyme that is expressed in testicular, adrenal, and prostatic tumor tissues. By inhibiting CYP17, abiraterone reduces the formation of testosterone...
The effectiveness of abiraterone was demonstrated in a study of approximately 1,200 patients with castration-resistant prostate cancer who had received previous chemotherapy containing docetaxel. The median overall survival was 14.8 months in the patients treated with abiraterone and prednisone compared with 10.9 months in the patients receiving placebo plus prednisone.

The inhibition of CYP17 by abiraterone also can result in increased mineralocorticoid production by the adrenals, and some patients experience hypokalemia (28%), edema (27%), and hypertension (9%) as a consequence. The concurrent use of prednisone suppresses adrenocorticotropic hormone drive and reduces the incidence and severity of these adverse events, but caution must be exercised in patients whose underlying medical conditions (e.g., heart failure, ventricular dysrhythmia) might be compromised by these responses. Patients should be monitored for hypertension, hypokalemia, and fluid retention at least once a month, and hypokalemia should be corrected and hypertension controlled before and during treatment with abiraterone.

Adrenocortical insufficiency was experienced by some patients treated with abiraterone and prednisone in the clinical studies; it was sometimes associated with interruption of daily steroids and/or concurrent infection or stress. The symptoms and signs of adrenocortical insufficiency may be masked by adverse events associated with mineralocorticoid excess. Patients should be monitored for this response, and increasing the dosage of corticosteroids before, during, and after stressful situations may be necessary.

Other commonly reported adverse events in the clinical studies of abiraterone included joint swelling/discomfort (30%), muscle discomfort (26%), hot flush (19%), diarrhea (18%), urinary tract infection (12%), cough (11%), urinary frequency (7%), nocturia (6%), upper respiratory tract infection (5%), and dysrhythmia (7%). The potential for prolongation of the QT interval of the electrocardiogram was evaluated, and no large changes from baseline were observed. However, small increases in the QT interval (i.e., <10 ms) cannot be excluded due to study design limitations.

Hepatotoxicity with elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin concentrations has been reported in some patients treated with abiraterone and may necessitate dosage modification or interruption or discontinuation of treatment. ALT, AST, and bilirubin concentrations should be determined before starting treatment, every 2 weeks for the first 3 months of treatment, and monthly thereafter.

Although prostate cancer is the only labeled indication for abiraterone, a potential exists for off-label use of the new drug for other conditions in women. The drug may cause fetal harm, is classified in Pregnancy Category X, and is contraindicated in women who are or may become pregnant. Women who are or may be pregnant should not handle the medication without protection such as gloves. Whether abiraterone or its metabolites are present in semen is unknown, and men being treated with the drug should use a condom if having sex with a pregnant woman and a condom plus another effective method of birth control if having sex with a woman of child-bearing potential. These precautions are required during and for 1 week after treatment with abiraterone.

The peak serum concentration and bioavailability of abiraterone are markedly increased when administered with food (i.e., 17-fold and 10-fold higher, respectively, when administered with a high-fat meal). Because of the variation in the composition and content of meals, and the resultant potential for highly variable and excessive exposures to the drug, no food should be consumed for at least 2 hours before the administration of abiraterone and for at least 1 hour after administration. The tablets should be swallowed whole with water.

Most of a dose of abiraterone is eliminated in the feces as the unchanged acetyl ester. Less than 5% of a dose is recovered in the urine. No dosage adjustment is needed in patients with renal impairment or mild hepatic impairment. The dosage should be reduced in patients with moderate hepatic impairment, and because the drug has not been studied in patients with severe hepatic impairment, it should not be used in these patients.

Abiraterone is a strong inhibitor of the CYP2D6 metabolic pathway, and concurrent use with CYP2D6 substrates with a narrow therapeutic index (e.g., thioridazine) should be avoided. If safer alternative medications are not available, a reduction in dosage of the CYP2D6 substrate should be considered and concurrent treatment should be closely monitored. Abiraterone is a substrate of CYP3A4, and the concurrent use of a strong CYP3A4 inhibitor (e.g., ketoconazole, clarithromycin) or inducer (e.g., carbamazepine, rifampin) should be avoided or used with caution.

The recommended dosage of abiraterone is 1,000 mg once a day. Food should not be consumed for at least 2 hours before and at least 1 hour after the dose of medication. Each tablet contains 250 mg abiraterone acetate, and the tablets should be swallowed whole with water. Abiraterone is used in a combination regimen with prednisone, and the dosage of the latter agent is 5 mg twice a day.

In patients with baseline moderate hepatic impairment, the recommended dosage of abiraterone is 250 mg once a day. ALT, AST, and bilirubin should be monitored before starting treatment, every week for the first month, every 2 weeks for the following 2 months of treatment, and monthly thereafter. If elevations in ALT and/or AST greater than five times the upper limit of normal (ULN) or total bilirubin greater than three times ULN occur in patients with baseline moderate hepatic impairment, treatment should be discontinued and not resumed.

For patients who develop hepatotoxicity during treatment (ALT and/or AST greater than five times ULN or total bilirubin...
greater than three times ULN), therapy should be interrupted. The product labeling should be consulted for the guidelines for restarting treatment and reductions in dosage.

Ipiilimumab

Melanoma is the most dangerous type of skin cancer and is the leading cause of death from skin disease. The number of cases has been increasing as a consequence, in part because of unprotected sun exposure earlier in life and the increased use of tanning salons. Almost 70,000 cases were diagnosed in the United States in 2010, and if identified at an early point, the condition is often curable. However, the prognosis for patients with late-stage (metastatic) melanoma is very poor, and approximately 8,700 Americans died from the disease in 2010. Treatment options for metastatic melanoma have been limited. Dacarbazine, carboplatin, temozolomide (Temodar), and aldesleukin (interleukin-2; Proleukin) have provided some benefit but have not been demonstrated to prolong survival.

Ipiilimumab (Yervoy—Bristol-Myers Squibb) is a recombinant human monoclonal antibody that binds to the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), which functions as a negative regulator of T-cell activation. By blocking the interaction of CTLA-4 with its ligands, ipilimumab increases T-cell activation and proliferation. Its benefit in patients with melanoma is indirect and thought to result from T-cell–mediated antitumor responses.

Ipiilimumab is administered by intravenous infusion and is indicated for the treatment of unresectable or metastatic melanoma. It is the first drug to be approved for the treatment of advanced melanoma in 13 years. Ipiilimumab was evaluated in patients who had been previously treated with one or more antineoplastic agents. One group of patients was treated with ipilimumab and an investigational peptide vaccine, a second group was treated with ipilimumab alone, and a third group received the vaccine alone. The primary efficacy outcome measure was overall survival. Median overall survival was 10.1 months in patients treated with the new drug alone, 10 months in the patients treated with ipilimumab plus the vaccine, and 6.4 months in the patients treated with the vaccine alone. Ipiilimumab is the first drug to be demonstrated to prolong survival in patients with metastatic melanoma and represents an important advance in the treatment of this condition.

Although the patients in the clinical trial had been treated with other antineoplastic agents before being treated with ipilimumab, its approval by FDA has not been limited to second-line use and it will often be used as first-line treatment. A second promising agent for the treatment of metastatic melanoma, vemurafenib (Zelboraf), was approved by FDA later in 2011. This agent inhibits the action of a mutation in a gene called BRAF™ that is present in the tumors of approximately one-half of the patients with advanced melanoma. It has been suggested that the combined use of ipilimumab and vemurafenib will provide clinical benefit that exceeds the benefit of either agent given alone, and such a study of the two agents is planned.

Because it causes T-cell activation and proliferation, the use of ipilimumab has been associated with severe and fatal immune-mediated adverse reactions, and this is the subject of a boxed warning in its labeling. The most common of these reactions are enterocolitis (e.g., bowel perforation), hepatitis, dermatitis (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis), neuropathies (e.g., Guillain-Barré syndrome, peripheral motor neuropathy), and endocrinopathies (e.g., hypopituitarism, hypothyroidism). Severe to fatal autoimmune reactions were experienced by 13% of the patients receiving the drug in the clinical study. Patients should be monitored for signs and symptoms of enterocolitis (e.g., diarrhea, abdominal pain), dermatitis (e.g., rash, pruritus), and neuropathy (e.g., motor or sensory neuropathy, paresthesias). Liver function and thyroid function tests should be determined at the start of treatment and before each dose. If severe adverse events occur, treatment with ipilimumab should be stopped and corticosteroid (e.g., prednisone) treatment initiated.

The most common adverse events experienced in the clinical studies of ipilimumab included fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%). The new drug is classified in Pregnancy Category C. Based on animal studies, it may cause fetal harm. Whether ipilimumab is excreted in human milk is not known, and a decision should be made whether to discontinue nursing or not use the drug. Its effectiveness and safety in pediatric patients have not been evaluated.

Ipiilimumab is administered intravenously over 90 minutes, and the recommended dosage is 3 mg/kg every 3 weeks for a total of 4 doses. The drug should be permanently discontinued if a severe or life-threatening adverse event occurs, if patients experience persistent moderate adverse events or an inability to reduce the dosage of the corticosteroid to 7.5 mg prednisone or equivalent per day, or if patients fail to complete the full treatment course within 16 weeks after administration of the first dose.

A scheduled dose of ipilimumab may be withheld in patients who experience moderate immune-mediated adverse events or symptomatic endocrinopathy. For patients with complete or partial resolution of adverse events and who are receiving less than 7.5 mg prednisone or equivalent per day, treatment with ipilimumab may be resumed at a dose of 3 mg/kg every 3 weeks until all four planned doses are administered or until 16 weeks after the first dose, whichever occurs earlier.

Ipiilimumab sterile solution is supplied in single-use vials containing 50 mg/10 mL and 200 mg/40 mL. The vials should be stored in a refrigerator, should be protected from light, and should not be shaken. Before preparing the infusion, the vial should be allowed to stand at room temperature for approximately 5 minutes. The volume of solution needed to provide the dose that has been determined should be withdrawn from the vial and transferred into an intravenous bag. This solution then should be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to prepare a solution with a final concentration ranging from 1 to 2 mg/mL. The diluted solution...
should be mixed by gentle inversion and used within 24 hours after preparation.

The approximate cost of ipilimumab for a patient weighing 70 kg is $120,000 for the course of treatment of four doses. Although this is the specific dosage regimen that has been initially approved for the drug, the use of the drug in a maintenance regimen for a longer period of time is being evaluated and has the likelihood of increasing the cost of treatment even further.

Agent for lipodystrophy in HIV-infected patients

Lipodystrophy is characterized by the development of excess fat in certain areas of the body, most often around the abdominal area. Also designated as fat redistribution syndrome, it has been associated with the use of antiretroviral agents in the treatment of patients with HIV infection. It is estimated that several hundred thousand Americans being treated with antiretroviral therapy experience accumulation of fat in areas such as the abdomen and upper back, while losing subcutaneous fat in the face, limbs, and buttocks. Visceral abdominal fat is a risk factor for cardiovascular disease, and concerns of patients about their appearance and being recognized as having HIV infection have been identified as reasons for which some patients are not adherent with their antiretroviral therapy regimens.

Tesamorelin acetate (Egrifta—Serono; Theratechnologies) has been approved for subcutaneous administration for the reduction of excess abdominal fat in HIV-infected patients with lipodystrophy. The new drug is an analog of human growth hormone–releasing factor (GRF), also known as growth hormone–releasing hormone, and is comprised of the 44–amino acid sequence of human GRF to which a hexenoyl moiety is attached. GRF is a hypothalamic peptide that stimulates the synthesis and pulsatile release of endogenous growth hormone, which is both anabolic and lipolytic. Tesamorelin binds with human GRF receptors and stimulates growth hormone secretion and subsequently insulin-like growth factor 1 (IGF-1) and insulin-like growth factor–binding protein 3.

Tesamorelin is the first drug to be approved for the treatment of lipodystrophy. Its effectiveness was evaluated in two studies in which the primary endpoint was the percent change from baseline to week 26 in visceral adipose tissue, as assessed by computed tomography scan, and the secondary endpoints included changes from baseline in patient-reported outcomes related to body image, lipid assessments, waist circumference, IGF-1 concentrations, and safety parameters. In both studies, patients treated with tesamorelin experienced greater reductions in abdominal fat compared with patients receiving placebo, and some patients reported improvements in their self-image. Patients who were treated with the new drug during the first 26 weeks of the study either continued receiving the drug or were switched to placebo during a second 26-week phase of the studies. The improvement in the study endpoints was maintained among the patients who continued to receive the medication, but the individuals who were switched to placebo experienced a rapid return to the degree of fat accumulation at baseline.

The use of tesamorelin was considered to have a weight-neutral effect, and it is not indicated for weight loss management. Neither the potential long-term cardiovascular benefit nor the long-term cardiovascular safety has been studied, and data are insufficient to determine whether the use of the drug improved adherence with antiretroviral therapy in patients with HIV. Tesamorelin also is being evaluated in studies in patients who are growth hormone deficient and abdominally obese and in patients with mild cognitive impairment. However, these are not labeled indications.

The use of tesamorelin is contraindicated in patients with disruption of the hypothalamic–pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumor/surgery, head irradiation, or head trauma. It is also contraindicated in patients with active malignancy (either newly diagnosed or recurrent) because it induces the release of endogenous growth hormone, a known growth factor. Any preexisting malignancy should be inactive and its treatment complete before initiating therapy with tesamorelin. The new drug also increases serum concentrations of IGF-1, another growth factor that may influence the development or progression of malignancies. IGF-1 concentrations should be monitored closely during treatment with tesamorelin.

During pregnancy, visceral adipose tissue increases due to normal metabolic and hormonal changes. Tesamorelin could cause fetal harm, and it is classified in Pregnancy Category X and contraindicated during pregnancy.

The adverse events most commonly reported in the clinical studies of tesamorelin included arthralgia (13%), injection site erythema (9%), injection site pruritus (8%), peripheral edema (6%), pain in extremity (6%), myalgia (6%), paresthesia (3%), and hypersensitivity reactions (4%). The occurrence of arthralgia, edema, and other musculoskeletal symptoms is probably associated with fluid retention that may result from the induction of growth hormone. These adverse events are usually transient or resolve with discontinuation of treatment. The use of tesamorelin also may be associated with the occurrence of glucose intolerance, and glucose status should be evaluated before starting treatment and monitored periodically during treatment.

Tesamorelin has not been studied in patients with acute critical illness, but complications have been associated with the use of growth hormone in patients who have had major surgery or have acute respiratory failure. Consideration should be given to discontinuing tesamorelin treatment in critically ill patients.

Whether tesamorelin is excreted in human milk is not known. However, HIV-infected mothers should not nurse their infants to avoid risking potential transmission of HIV infection. The effectiveness and safety of tesamorelin in pediatric patients have not been established. The new drug should not be used in children with open epiphyses because excess growth hormone and IGF-1 may result in linear growth acceleration and excessive growth.
As with other therapeutic proteins and peptides, the development of anti-tesamorelin antibodies is possible. Such antibodies were detected in approximately 50% of patients treated with the drug and in about 85% of the patients who experienced hypersensitivity reactions. In the patients in whom neutralizing antibodies were detected, the presence of the antibodies did not appear to alter the effectiveness of the drug.

Growth hormone has been reported to alter the clearance of medications that are metabolized by CYP450 liver enzymes and to inhibit 11-beta-hydroxysteroid dehydrogenase type 1, a microsomal enzyme required for the conversion of cortisol to its active metabolite (cortisol) in hepatic and adipose tissue. Because tesamorelin stimulates growth hormone production, patients receiving glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in maintenance or stress doses following initiation of treatment with the new drug.

Tesamorelin acetate is supplied in single-use vials in an amount equivalent to 1 mg tesamorelin base. The vials should be stored in a refrigerator and protected from light and kept in the original box until time of use. Vials of diluent (Sterile Water for Injection) are supplied with the vials of medication. Following reconstitution, the concentration of the drug is 1 mg/mL, and the solution should be injected immediately. Tesamorelin is administered subcutaneously and the recommended dosage is 2 mg once a day. The abdomen is the recommended injection site, and injection sites should be rotated to different areas of the abdomen.

Pediculicide
Head lice infestation is most commonly experienced by school-age children. Although the nonprescription agents permethrin (e.g., Nix) and pyrethrins with piperonyl butoxide (e.g., RID) have been widely and effectively used for treatment, increasing resistance to these agents has been reported. Other pediculicides that have been applied topically for the treatment of head lice infestation include malathion (Ovide) and benzyl alcohol (Ulesfia), both of which require a prescription.

Spinosad (Natroba—ParaPRO) is a pediculicide that is derived from the fermentation of a soil actinomycete bacterium, Saccharopolyspora spinosa. It is a mixture of spinosyn A and spinosyn D in a ratio of approximately 5 to 1. Spinosad causes neuronal excitation in insects, and after periods of hyperexcitation, lice become paralyzed and die.

Spinosad is indicated for the topical treatment of head lice infestation in patients 4 years or older. Its effectiveness has been demonstrated in two studies in which it was compared with permethrin (1%). Patients were treated and returned 7 days later for efficacy evaluation. Patients in whom live lice were identified on day 7 received a second treatment. Efficacy was assessed as the proportion of participants who were free of live lice 14 days after the final treatment. Spinosad was effective in 85% and 87% of the patients in studies 1 and 2, respectively, compared with 45% and 43% of the patients treated with permethrin. More of the permethrin-treated patients required two treatments compared with the spinosad-treated patients.

Pyrethrins with piperonyl butoxide also are approved for treating pubic lice and body lice infestation, and permethrin also is approved for treating scabies. However, these are not labeled indications for spinosad at the present time.

The topical application of spinosad is well tolerated, and the most commonly reported adverse events included application site erythema (3%), ocular erythema (2%), and application site irritation (1%). Its effectiveness and safety have not been established in children younger than 4 years, and the labeling includes a warning against use in neonates and infants younger than 6 months. The suspension formulation of spinosad includes benzyl alcohol, systemic exposure to which has been associated with serious reactions ("gasping syndrome") and deaths in neonates and low-birth-weight infants.

Spinosad is classified in Pregnancy Category B. It is not systemically absorbed and, therefore, will not be present in human milk. However, benzyl alcohol may be absorbed through the skin, although the amount that may be excreted in human milk is not known. Caution must be exercised if spinosad is used by a lactating woman. A lactating woman may choose to pump and discard breast milk for 8 hours (5 half-lives of benzyl alcohol) after use to avoid infant ingestion of benzyl alcohol.

Spinosad topical suspension contains the drug in a concentration of 0.9% and is supplied in 120-mL bottles. The suspension should be shaken well before use, and a sufficient amount should be applied to cover the dry scalp and then applied to dry hair. Depending on the length of the hair, up to 120 mL may be needed to adequately cover the scalp and hair. The patient’s face and eyes should be covered with a towel, and the eyes should be closed tightly during application. The suspension should be left on the hair for 10 minutes and then thoroughly rinsed off with warm water. A fine-tooth comb may be used to remove treated lice and nits from the hair and scalp, but combing is not required. If live lice are observed 7 days after the first treatment, a second treatment should be applied.

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

Instructions: This exam must be taken online; please see “CPE information” below for further instructions. There is only one correct answer to each question. This CPE activity will be available online at www.pharmacist.com no later than November 30, 2011.

1. Which of the following agents must be administered apart from food?
   a. Boceprevir
   b. Telaprevir
   c. Roflumilast
   d. Abiraterone

2. Which of the following agents is administered subcutaneously?
   a. Abiraterone
   b. Ipilimumab
   c. Tesamorelin
   d. Spinosad

3. Which of the following agents is administered three times a day?
   a. Boceprevir
   b. Roflumilast
   c. Abiraterone
   d. Tesamorelin

4. Which of the following agents acts as an inhibitor of the enzyme phosphodiesterase 4?
   a. Telaprevir
   b. Roflumilast
   c. Abiraterone
   d. Tesamorelin

5. Which of the following agents is most likely to be associated with the occurrence of enterocolitis?
   a. Boceprevir
   b. Tesamorelin
   c. Ipilimumab
   d. Abiraterone

6. Which of the following agents has been associated with the occurrence of drug rash with eosinophilia and systemic symptoms?
   a. Telaprevir
   b. Boceprevir
   c. Spinosad
   d. Roflumilast

7. Which of the following agents is most likely to be associated with weight loss?
   a. Telaprevir
   b. Tesamorelin
   c. Abiraterone
   d. Roflumilast

8. Which of the following statements is correct regarding boceprevir?
   a. Its greatest value is in patients with hepatitis C virus (HCV) infection who have been classified as null responders.
   b. It may be used as a single agent in patients with HCV infection that is resistant to peginterferon alfa and ribavirin.
   c. It is classified in Pregnancy Category X.
   d. When used in a patient who is also taking sildenafil, the dosage of sildenafil should be reduced.

9. Which of the following statements is correct regarding boceprevir?
   a. Anemia is one of the most common adverse events associated with its use.
   b. Its action may be increased by the concurrent use of St. John’s wort.
   c. Its dosage should be reduced in patients with renal impairment.
   d. It is used in a three-drug regimen with peginterferon alfa and ribavirin for 48 weeks.

CPE information

To obtain 2.0 contact hours of CPE credit (0.2 CEUs) for this activity, complete and submit the CPE exam online at www.pharmacist.com/education. A Statement of Credit will be awarded for a passing grade of 70% or better. You will have two opportunities to successfully complete the CPE exam. Pharmacists who successfully complete this activity before November 15, 2014, can receive credit.

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Live step-by-step assistance is available Monday through Friday 8:30 am to 5:00 pm ET at APhA Member Services at 800-237-APhA (2742) or by e-mailing InfoCenter@pharmacist.com.
10. Which of the following statements is correct regarding telaprevir?
   a. It is used concurrently with peginterferon alfa and acyclovir.
   b. Many patients experience elevated uric acid concentrations during treatment.
   c. It is excreted in unchanged form in the urine.
   d. It is classified as an HCV polymerase inhibitor.

11. Which of the following statements is correct regarding telaprevir?
   a. It should only be used in patients with HCV infection that has not been previously treated.
   b. Its use is not recommended in patients with moderate or severe hepatic impairment.
   c. It should be added to the antiviral regimen after peginterferon alfa has been used for a period of 4 weeks.
   d. Treatment should be continued for a period of 48 weeks.

12. Which of the following statements is correct regarding roflumilast?
   a. It has been approved for the treatment of patients with severe chronic obstructive pulmonary disease associated with emphysema.
   b. It is classified as a bronchodilator.
   c. Psychiatric adverse events have been associated with its use.
   d. It is available in a combination formulation with a corticosteroid.

13. Which of the following statements is correct regarding roflumilast?
   a. Its labeled indications include use for the treatment of acute bronchospasm.
   b. It is excreted in unchanged form in the urine.
   c. Its action may be increased by the concurrent use of a cytochrome P450 (CYP)3A4 inhibitor.
   d. Its use is contraindicated in patients with impaired renal function.

14. Which of the following statements is correct regarding abiraterone?
   a. It is indicated for the treatment of pancreatic cancer.
   b. It is classified as a gonadotropin-releasing hormone agonist.
   c. Hyperkalemia is a common adverse event associated with its use.
   d. It should be used in combination with prednisone.

15. Which of the following statements is correct regarding abiraterone?
   a. Liver function tests should be determined prior to starting treatment and periodically during treatment.
   b. Its bioavailability is markedly decreased when it is administered with food.
   c. Its dosage should be reduced in patients with renal impairment.
   d. Its action may be reduced by the concurrent administration of clarithromycin.

16. Which of the following statements is correct regarding ipilimumab?
   a. It is a prodrug that is converted to its active form following administration.
   b. It increases T-cell activation and proliferation.
   c. It inhibits the action of a mutation in the BRAF gene.
   d. It is used in combination with a peptide vaccine.

17. Which of the following statements is correct regarding ipilimumab?
   a. It prolongs survival in patients with castration-resistant prostate cancer.
   b. It is administered once a week for 8 weeks.
   c. It is a substrate for the CYP3A4 metabolic pathway.
   d. Immune-mediated adverse reactions are the most important concern associated with its use.

18. Which of the following statements is correct regarding tesamorelin?
   a. It is an analog of human growth hormone-releasing factor.
   b. It is classified as a monoclonal antibody.
   c. It is used in the treatment of muscle redistribution syndrome.
   d. It is effective in increasing weight in patients with debilitating diseases.

19. Which of the following statements is correct regarding tesamorelin?
   a. Peripheral neuropathy is the most common adverse event associated with its use.
   b. Treatment should not be continued for longer than 12 weeks because of the likelihood that neutralizing antibodies will develop that will reduce its effect.
   c. Its use is contraindicated in patients with active malignancy.
   d. It is extensively metabolized via the CYP2D6 pathway.

20. Which of the following statements is correct regarding spinosad?
   a. It is indicated for use in patients 4 months or older.
   b. It was more effective than permethrin in comparative clinical studies.
   c. Its labeled indications include head lice infestation and scabies.
   d. It should be applied once a week for up to a maximum of four treatments.