Abstract

Objective: To provide information about the most important properties of new FDA-approved therapeutic agents marketed in 2016.

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

Data synthesis: The first part of this four-part series covers eight new FDA-approved therapeutic agents marketed in the United States in early 2016: elbasvir/grazoprevir, velpatasvir/sofosbuvir, pimavanserin tartrate, brivaracetam, reslizumab, ixekizumab, and patiromer sorbitex calcium. The authors review indications, mechanisms of action, and information on dosage and administration of these new agents, as well as their most important pharmacokinetic properties, adverse events, and other risks and precautions. They compare the new agents with older drugs marketed for the same indications and identify their advantages and disadvantages.

Summary: Elbasvir and grazoprevir, new direct-acting antiviral agents with activity against hepatitis C virus (HCV), are used in a combination formulation for treatment of chronic HCV infection. Velpatasvir is used with sofosbuvir in a combination formulation for treatment of chronic HCV infection. Pimavanserin is the first antipsychotic agent to be approved for treatment of hallucinations and delusions associated with Parkinson disease psychosis. Brivaracetam, an antiepileptic drug that is an analog of levetiracetam, is indicated as adjunctive therapy in treatment of partial-onset seizures. Reslizumab, a monoclonal antibody that acts as an interleukin-5 antagonist, is indicated as add-on maintenance treatment of patients with severe asthma and an eosinophilic phenotype. Ixekizumab, an interleukin-17A antagonist, is administered subcutaneously for treatment of moderate to severe plaque psoriasis. Patiromer sorbitex calcium, which binds with potassium in the gastrointestinal tract, is indicated in treatment of hyperkalemia.
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 drug: use pairings is correct?
   a. Pimavanserin: depression
   b. Brivaracetam: psoriasis
   c. Patiromer: hyperkalemia
   d. Ixekizumab: asthma

2. Which of the following agents is administered twice daily?
   a. Elbasvir/grazoprevir
   b. Velpatasvir/sofosbuvir
   c. Pimavanserin
   d. Brivaracetam

3. Which of the following statements is correct about velpatasvir/sofosbuvir?
   a. Dosage adjustment is not necessary in patients with hepatic impairment.
   b. Its action may be increased by concurrent use of a cytochrome P450 (CYP) 3A inducer.
   c. It is administered three times daily.
   d. Duration of treatment is 8 weeks in patients who do not have cirrhosis.

Objective
This review covers eight new FDA-approved therapeutic agents marketed in 2016, although two of these drugs, elbasvir and grazoprevir, are used in a combination formulation and are not available as single agents (Table 1). Following the discussion of each new therapeutic agent, the authors compare the new drug to the older medication(s) with which it is most similar in properties and uses and identify its most important advantages and disadvantages. Advantages and disadvantages are identified at the time the new drug was first marketed and do not reflect the approval of additional new drugs and/or other changes that occurred subsequent to initial marketing.

Antiviral agents
Marketing of sofosbuvir (Sovaldi—Gilead Sciences) in late 2013 and a combination of ledipasvir and sofosbuvir (Harvoni—Gilead Sciences) in late 2014 represented very important advances in treatment of chronic hepatitis C virus (HCV) infection, with cure rates exceeding 90%. Ledipasvir/sofosbuvir was initially approved for treatment of patients with chronic HCV genotype 1 infection, the most common genotype in the United States, and subsequently approved for treatment of patients with chronic HCV genotypes 4, 5, and 6 infections.

Ledipasvir/sofosbuvir is administered once daily for 12 weeks for most patients, although an 8-week course of treatment can be considered for treatment-naïve patients with genotype 1 infection without cirrhosis who have pretreatment HCV RNA of less than 6 million IU/mL. In some patients (e.g., treatment-naïve and treatment-experienced with decompensated cirrhosis), ribavirin is included in the treatment regimen.

A second combination formulation (Viekira Pak—AbbVie), also approved in 2014, includes tablets containing ombitasvir, paritaprevir, and ritonavir that are copackaged with dasabuvir tablets. This regimen is indicated for patients with chronic HCV genotype 1 infection, and patients with genotype 1a infection should also be treated with ribavirin. The tablets containing ombitasvir, paritaprevir, and ritonavir are administered once daily, and the tablets containing dasabuvir are administered twice daily, usually for 12 weeks. In July of 2016, FDA approved Viekira XR extended-release tablets that include the four active components of Viekira Pak in a formulation administered once daily with food.

Subsequently, the combination of ombitasvir, paritaprevir, and ritonavir (Technivie—AbbVie) was approved for use with ribavirin for treatment of patients with chronic HCV genotype 4 infection without cirrhosis. Like ledipasvir/sofosbuvir, these combination regimens are highly effective. However, inclusion of ritonavir, a strong cytochrome P450 (CYP) 3A4 inhibitor, to increase paritaprevir’s concentration and duration of action significantly increases the potential for interactions with numerous other medications.

In 2015, daclatasvir (Daklinza—Bristol–Myers Squibb) was the next antiviral agent to be approved for treatment of patients with chronic HCV infection, initially for treatment of genotype 3 infection and subsequently for genotype 1 infection. It is specifically indicated for use with sofosbuvir, with or without ribavirin, for treatment of patients with chronic HCV genotype 1 or 3 infection. However, it is less effective in patients with genotype 3 infection with cirrhosis. Unlike the ledipasvir/sofosbuvir and ombitasvir/paritaprevir/ritonavir plus dasabuvir regimens, in which the components of the formulations have been developed by the same companies, daclatasvir and sofosbuvir are marketed by different companies, and the treatment regimen is much more expensive.

Two new combination formulations of antiviral agents for treatment of chronic HCV infection have been marketed in 2016: elbasvir/grazoprevir (Zepatier—Merck) for patients with chronic HCV genotypes 1 or 4 infection, and velpatasvir/sofosbuvir (Epclusa—Gilead) for patients with chronic HCV genotypes 1, 2, 3, 4, 5, or 6 infection. Antiviral agents approved for chronic HCV infection inhibit enzymes/proteins that are essential for HCV replication. Elbasvir and velpatasvir are HCV NS5A inhibitors with properties that are most similar to those of ledipasvir, ombitasvir, and daclatasvir. Grazoprevir is an HCV NS3/4A protease inhibitor with properties that are most similar to those of simeprevir (Olysio—Janssen Therapeutics) and paritaprevir. Sofosbuvir is a nucleotide analog NS5B inhibitor, and dasabuvir is a nonnucleoside NS5B palm polymerase inhibitor.

The elbasvir/grazoprevir and velpatasvir/sofosbuvir combinations are considered individually in the following discussions. Some of the recommended treatment regimens of the new combination products, as well as several other
treatment regimens for chronic HCV infection, also include ribavirin. Therefore, caution must be exercised with respect to the risks and warnings associated with use of this agent. Of particular importance is the potential for ribavirin to cause teratogenic and/or embryocidal effects; its use is contraindicated in pregnant women and their male partners. Ribavirin has a long half-life and may not be completely eliminated for as long as 6 months. Pregnancy must be avoided during treatment and for 6 months following completion of treatment, and at least two reliable forms of effective contraception must be used during this period.

**Elbasvir/grazoprevir**

Elbasvir/grazoprevir (Zepatier—Merck), a fixed-dose combination product, is indicated for treatment of adult patients with chronic HCV genotypes 1 or 4 infection. In some patients, ribavirin is also included in the treatment regimen. It is contraindicated in patients with moderate or severe hepatic impairment because of the expected significantly increased grazoprevir plasma concentration and an increased risk of alanine aminotransferase (ALT) elevations. Accordingly, hepatic laboratory testing should be conducted before treatment initiation and during treatment. Patients with genotype 1a infection should also be tested before treatment initiation for the presence of virus with NS5A resistance-associated polymorphisms (i.e., at amino acid positions 28, 30, 31, or 93), because this factor determines whether ribavirin should be included in the regimen, as well as the treatment duration.

Effectiveness of elbasvir/grazoprevir was evaluated in two placebo-controlled trials and four uncontrolled trials in which sustained virologic response (SVR) was the primary endpoint, defined as HCV RNA less than the lower limit of quantification at 12 weeks following cessation of treatment (SVR12). Overall SVR rates ranged from 94% to 97% in patients with genotype 1 infection and from 97% to 100% in patients with genotype 4 infection.

Adverse events most often reported in the placebo-controlled clinical trials included fatigue (11%) and headache (10%). In patients who were also treated with ribavirin and for a longer time period (16 weeks, compared with 12 weeks for most patients), adverse events experienced most often were anemia (8%) and headache (6%). ALT elevations from normal concentrations to greater than 5 times the upper limit of normal (ULN) occurred in 1% of patients. In patients receiving a 12-week course of treatment, hepatic laboratory testing should be performed before starting therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12. Treatment discontinuation should be considered if ALT concentrations remain persistently greater than 10 times the ULN. If the ALT elevation is accompanied by signs or symptoms of liver inflammation, such as fatigue, weakness, lack of appetite, nausea, and vomiting, as well as later signs, such as jaundice and discolored feces.

Safety of elbasvir/grazoprevir has not been evaluated in pregnant women. However, adverse effects on fetal development have not been observed in animal studies. In addition, effectiveness and safety have not been established in patients younger than 18 years of age.

Elbasvir/grazoprevir may be administered without regard to food. Both drugs undergo metabolism, primarily via the CYP3A pathway, and more than 90% of a dose is eliminated in the feces. Dosage adjustment is not necessary in patients with renal impairment, including hemodialysis, or in patients with mild hepatic impairment.

Plasma concentrations and antiviral action of elbasvir/grazoprevir may be significantly reduced by strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort) and efavirenz, and concurrent use is contraindicated. In addition, concurrent use of a moderate CYP3A inducer (e.g., bosentan, etravirine, modafanil, nafcillin) is not recommended. Conversely, elbasvir/grazoprevir’s action may be increased by CYP3A inhibitors such as ketoconazole, as well as certain

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*aFDA classification of new drugs: 1 = new molecular entity; 4 = combination product; S = standard review; P = priority review.

*bBiological approved through an FDA procedure that does not assign a numerical classification.
combination products for HIV infection (e.g., Striibl—Gilead Sciences), and concurrent use is not recommended.

Elbasvir/grazoprevir may increase the concentration and activity of tacrolimus, so concurrent use should be closely monitored. Concentrations of atorvastatin and rosuvastatin may be increased by concurrent use of elbasvir/grazoprevir, and daily doses of 20 mg and 10 mg, respectively, of the lipid-regulating drugs should not be exceeded. Concentrations of fluvastatin, lovastatin, and simvastatin may also increase, so concurrent use with elbasvir/grazoprevir should be closely monitored.

Grazoprevir is a substrate of organic anion-transporting polypeptides (OATP) 1B1/3. Because its plasma concentration and risk of ALT elevations may be significantly increased by OATP 1B1/3 inhibitors (e.g., cyclosporine, atazanavir, darunavir, lopinavir, saquinavir, tipranavir), concurrent use is contraindicated. Elbasvir/grazoprevir tablets contain 50 mg of elbasvir and 100 mg of grazoprevir. They are packaged in a carton containing 28 tablets in two 14-count child-resistant dose packs. To protect from moisture, the product should be stored in the original blister package until use.

Recommended dosage of elbasvir/grazoprevir is one tablet once daily with or without food. Recommended duration of treatment is 12 weeks in patients with the following types of infections/experiences: genotype 1a (treatment-naive or peginterferon alfa/ribavirin–experienced without baseline NS5A polymorphisms), genotype 1b (treatment-naive or peginterferon alfa/ribavirin–experienced), genotype 4 (treatment-naive), and (with ribavirin) in patients with genotypes 1a or 1b who are peginterferon alfa/ribavirin/HCV protease inhibitor (e.g., simeprevir)–experienced. Elbasvir/grazoprevir should be used with ribavirin for 16 weeks in patients with genotype 1a infection who are treatment-naive or peginterferon alfa/ribavirin–experienced with baseline NS5A polymorphisms and in patients with genotype 4 infection who are peginterferon alfa/ribavirin–experienced. The same dosage recommendations should be followed for patients with HCV infection who are coinfected with HIV-1.

### Comparison of elbasvir/grazoprevir with ledipasvir/sofosbuvir

**Advantages**
- May be safer in patients with impaired renal function
- Less likely to cause bradycardia in patients treated with amiodarone

**Disadvantages**
- Labeled indications are more limited (ledipasvir/sofosbuvir is also indicated for HCV genotypes 5 and 6 infections)
- Patients with genotype 1a infection should be tested for NS5A resistance–associated polymorphisms
- Contraindicated in patients with moderate or severe hepatic impairment
- More likely to cause hepatic adverse events, and liver function tests should be monitored
- Contraindicated in patients treated with a strong CYP3A inducer, efavirenz, or an organic anion-transporting polypeptide (OATP) 1B1/3 inhibitor

### Velpatasvir/sofosbuvir

Velpatasvir/sofosbuvir (Epclusa—Gilead), a fixed-dose combination product for adult patients with chronic HCV, is the first agent to be approved for treatment of all six major HCV genotype infections (1, 2, 3, 4, 5, or 6).

It is not indicated for patients without cirrhosis or with compensated cirrhosis. It should be used in combination with ribavirin in patients with decompensated cirrhosis (i.e., moderate to severe cirrhosis).

Effectiveness of velpatasvir/sofosbuvir was evaluated in three clinical trials in treatment-naive and treatment-experienced patients without cirrhosis or with compensated cirrhosis (mild cirrhosis). One study included patients with HCV genotypes 1, 2, 4, 5, or 6 infection, another study included patients with genotype 2 infection, and the third study included patients with genotype 3 infection. SVR rates were 95% to 99% at 12 weeks following a 12-week course of treatment. In another study, patients with HCV infection of all six genotypes and with decompensated cirrhosis were treated with velpatasvir/sofosbuvir and ribavirin. SVR rate was 94% at 12 weeks following a 12-week course of treatment. Effectiveness of velpatasvir/sofosbuvir in treating patients with chronic HCV infections of all six genotypes is of particular importance in patients with genotype 2 or 3 infection, in whom previous treatment options were limited and/or even more costly. In addition, it may not be necessary to perform genotype testing in situations in which resources are not readily available.

Adverse events reported most often in the studies in patients without cirrhosis or with compensated cirrhosis included headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%), although the frequency of these events was similar in patients receiving placebo. In patients with uncompensated cirrhosis who were also treated with ribavirin, the most commonly experienced adverse events included fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%).

Symptomatic bradycardia has been reported in patients taking amiodarone concurrently with a sofosbuvir-containing regimen, and some have required pacemaker intervention. Patients also taking beta-blockers, or those with underlying cardiac comorbidities and/or advanced liver disease, may be at increased risk for this response when amiodarone is administered concurrently with velpatasvir/sofosbuvir. Concurrent therapy is not recommended, but if no other viable treatment option is available, the drugs may be used concomitantly with cardiac monitoring in an inpatient setting for the first 48 hours of coadministration, after which outpatient or self-monitoring of the heart rate should occur daily through at least the first 2 weeks of treatment. Because amiodarone has a long half-life, patients discontinuing this drug just before treatment initiation with velpatasvir/sofosbuvir should also undergo similar cardiac monitoring. Patients should be advised to immediately seek medical evaluation if they experience signs or symptoms of bradycardia (e.g., dizziness, lightheadedness, fainting,
weakness, shortness of breath).

Safety of velpatasvir/sofosbuvir has not been evaluated in women who are pregnant. However, adverse effects on fetal development have not been observed in animal studies. Effectiveness and safety of the new product have not been established in patients younger than 18 years of age.

Velpatasvir undergoes limited metabolism via the CYP2B6, CYP2C8, and CYP3A4 pathways, and almost all of a dose is excreted in the feces, primarily via biliary excretion of the parent compound. Sofosbuvir is rapidly converted to its primary circulating active nucleoside metabolite, GS-331007. More than 80% of a dose of sofosbuvir is excreted in the urine. Dosage adjustment is not necessary in patients with hepatic impairment, although clinical and hepatic laboratory monitoring, as clinically indicated, are recommended for patients with decompensated cirrhosis who are being treated with velpatasvir/sofosbuvir and ribavirin. Dosage adjustment is not necessary in patients with mild or moderate renal impairment. However, safety of the new product has not been established in patients with severe renal impairment or with end-stage renal disease requiring hemodialysis, and dosage recommendations are not provided.

Velpatasvir and sofosbuvir are substrates for drug transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), whereas GS-331007 is not. Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., carbamazepine, rifampin, St. John’s wort, efavirenz) may reduce the therapeutic benefit of velpatasvir/sofosbuvir, and concurrent use is not recommended. Activity of velpatasvir/sofosbuvir may also be reduced by tipranavir/ritonavir, and concomitant use is not recommended.

Velpatasvir/sofosbuvir has been reported to increase concentrations of topotecan, digoxin, tenofovir (e.g., Viread—Gilead Sciences), rosvastatin, and atorvastatin. Concurrent use with topotecan is not recommended, and use with the other agents should be closely monitored for potential adverse events. The daily dosage of rosvastatin should not exceed 10 mg when used concurrently with velpatasvir/sofosbuvir.

Solubility of velpatasvir decreases as pH increases, and drugs that increase gastric pH may decrease its concentration and activity. Administration of velpatasvir/sofosbuvir and an antacid should be separated by an interval of at least 4 hours. A histamine-2 (H2) receptor antagonist may be administered simultaneously with or 12 hours apart from velpatasvir/sofosbuvir at a dose that does not exceed dosages comparable to 40 mg of famotidine twice daily. Concurrent use of a proton pump inhibitor with velpatasvir/sofosbuvir is not recommended. However, if it is considered medically necessary to use both products, velpatasvir/sofosbuvir should be administered with food and taken 4 hours before omeprazole in a 20-mg dose. Use of velpatasvir/sofosbuvir with other proton pump inhibitors has not been studied.

Velpatasvir/sofosbuvir tablets contain 100 mg of velpatasvir and 400 mg of sofosbuvir. Each bottle contains 28 tablets that should be dispensed in the original container.

Recommended dosage of velpatasvir/sofosbuvir is one tablet once daily with or without food. In patients with chronic HCV infection with decompensated cirrhosis, ribavirin should also be included in the treatment regimen. Duration of treatment with velpatasvir/sofosbuvir, with or without ribavirin, is 12 weeks, which provides an advantage when compared with regimens for other medications that are 16 weeks, 24 weeks, or longer for certain HCV infections. However, the ledipasvir/sofosbuvir regimen may be used for just an 8-week period in treatment-naive patients with HCV genotype 1 infection without cirrhosis who have pretreatment HCV RNA of less than 6 million IU/mL.

**Comparison of velpatasvir/sofosbuvir with ledipasvir/sofosbuvir and elbasvir/grazoprevir**

**Advantages**

- First product to be approved for treatment of HCV infection of all six major genotypes
- Chronic HCV genotypes 2 and 3 infection included in labeled indications
- Ribavirin not needed in treatment regimen in as many types of infections or situations (compared with elbasvir/grazoprevir used in combination with ribavirin in treatment-experienced patients)
- Not necessary to test patients with genotype 1a infection for NS5A resistance-associated polymorphisms (compared with elbasvir/grazoprevir)
- Safer in patients with impaired hepatic function (compared with elbasvir/grazoprevir)
- Treatment duration of 12 weeks in all patients (whereas ledipasvir/sofosbuvir treatment is continued for 24 weeks in some patients, and elbasvir/grazoprevir treatment is continued for 16 weeks in some patients).

**Disadvantages**

- Experience more limited in patients with HIV-1 coinfection
- Safety not established in patients with severe renal impairment (compared with elbasvir/grazoprevir, which may be used without dosage adjustment)
- May cause bradycardia in patients treated with amiodarone (compared with elbasvir/grazoprevir)
- Shortest treatment period is 12 weeks (compared with ledipasvir/sofosbuvir, which may be used for an 8-week period in some treatment-naive patients with genotype 1 infection without cirrhosis)

**Antipsychotic agent: Pimavanserin tartrate**

Approximately 1 million Americans have Parkinson disease (PD), and an estimated 50,000 individuals are diagnosed with the disease each year. Most patients experience tremors as an early manifestation of PD and, as the condition worsens, the increasing severity of the tremors may interfere with daily activities (e.g., writing, eating). As many as 50% of patients with PD experience psychosis (e.g., hallucinations, delusions), and this is a major reason for nursing home admissions of patients with the disease.

PD is characterized by a reduction in dopamine activity, and a goal of treatment with medications such as levodopa is to increase dopamine concentrations and activity. Psychosis
in a patient with PD presents a formidable treatment challenge because most antipsychotic drugs exhibit a dopamine antagonist action and may cause extrapyramidal (PD-like) effects that compromise the benefits of dopaminergic medications prescribed for PD.

Serotonin 5-hydroxtryptamine$_{2A}$ (5-HT$_{2A}$) receptors are thought to play an important role in PD psychosis. Pimavanserin tartrate (Nuplazid—Acadia) is the first drug to be approved specifically for treatment of hallucinations and delusions associated with PD psychosis. This atypical antipsychotic agent has a unique mechanism of action: it preferentially targets 5-HT$_{2A}$ receptors, and its action is mediated through a combination of inverse agonist and antagonist activity at these receptors. Unlike other antipsychotic drugs, it does not act at dopamine receptors; therefore, it does not interfere with patients’ dopaminergic therapy or impair motor function.

FDA granted pimavanserin a breakthrough therapy designation, an initiative established to expedite the development and review of drugs that are intended to treat a serious condition and where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy.

Pimavanserin is metabolized to a major active metabolite. Its effectiveness was evaluated in a 6-week placebo-controlled study that included 199 patients. A PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) was used to evaluate efficacy. This nine-item scale was adapted for PD from the Hallucinations and Delusions domains of the SAPS. The new drug was demonstrated to be superior to placebo in decreasing the frequency and/or severity of both hallucinations and delusions, without worsening the primary motor symptoms of PD.

As with the other atypical antipsychotic agents, labeling for pimavanserin includes a boxed warning about an increased risk of death in seniors with dementia-related psychosis. The new drug is not approved for treatment of dementia-related psychosis that is unrelated to the hallucinations and delusions associated with PD psychosis.

Pimavanserin prolongs the QT interval and may increase the risk of cardiac arrhythmias. Its use should be avoided in patients with known QT prolongation and/or a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of torsade de pointes and/or sudden death, including symptomatic bradycardia, hypokalemia, or hypomagnesemia. It should not be used concurrently with other medications known to prolong the QT interval, including Class 1A antiarrhythmics (e.g., quinidine, procainamide, disopyramide), Class 3 antiarrhythmics (e.g., amiodarone, sotalol), certain antipsychotic medications (e.g., ziprasidone, chlorpromazine, thioridazine), and certain antibacterial agents (e.g., moxifloxacin).

Adverse events most often reported in the clinical studies included nausea (7%), peripheral edema (7%), and confusional state (6%). The drug’s unique mechanism may be associated with a lower risk of certain serious adverse events (e.g., tardive dyskinesia, neuroleptic malignant syndrome) that have been infrequently experienced with other antipsychotic drugs.

Pimavanserin may be administered with or without food. It is extensively metabolized, primarily via the CYP3A4 pathway, and almost the entire dose is eliminated in the form of metabolites. Dosage adjustment is not necessary in patients with mild to moderate renal impairment. However, pimavanserin has not been evaluated in patients with severe renal impairment or with any degree of hepatic impairment, and its use is not recommended in these patients.

Concurrent use of a strong CYP3A4 inhibitor (e.g., clarithromycin, itraconazole, ketoconazole) may increase pimavanserin’s exposure and activity, and the dosage of the new drug should be reduced. Conversely, concurrent use of a strong CYP3A4 inducer (e.g., carbamazepine, phenytoin, rifampin, St. John’s wort) may reduce pimavanserin’s exposure and effectiveness, and an increase in dosage may be necessary.

The recommended dosage of pimavanserin is 34 mg (two tablets) once a day. In patients being treated concurrently with a strong CYP3A4 inhibitor, the recommended dosage is 17 mg (one tablet) once a day. The film-coated tablets in which the drug is supplied contain 20 mg of pimavanserin tartrate, which is equivalent to 17 mg of pimavanserin free base.

### Comparison of pimavanserin tartrate with atypical antipsychotic agents (e.g., risperidone)

#### Advantages
- First drug to be approved for treatment of hallucinations and delusions associated with PD psychosis
- Unique mechanism of action (a combination of inverse agonist and antagonist activity at serotonin 5-HT$_{2A}$ receptors)
- Does not act at dopamine receptors and not likely to cause extrapyramidal effects
- May be less likely to cause serious adverse events (e.g., tardive dyskinesia, neuroleptic malignant syndrome)

#### Disadvantages
- More likely to cause QT interval prolongation and increased risk of arrhythmias (the atypical antipsychotic agent ziprasidone is also associated with a higher risk level)

### Antiepileptic agent: Brivaracetam

Approximately 5 million people in the United States have a history of epilepsy, and almost 3 million have active epilepsy. Partial-onset seizures, the most common type of epilepsy, affect a limited or localized area of the brain but can spread to other parts of the brain.

Brivaracetam (Briviact—UCB Pharma), indicated as adjunctive therapy in treatment of partial-onset seizures in patients 16 years of age and older with epilepsy, is an analog of levetiracetam (e.g., Keppra—UCB Pharma). Both agents’ effectiveness in treatment of seizure disorders is thought to be due to their affinity for synaptic vesicle protein 2A in the brain. They may be administered orally or intravenously.

Brivaracetam’s effectiveness in reducing seizure frequen-
Brivaracetam is demonstrated in three placebo-controlled trials in 1,550 patients who were also taking other antiepileptic drugs (AEDs) concomitantly. In the study in which brivaracetam was evaluated in dosages of 100 mg/d and 200 mg/d, both dosages resulted in an approximately 25% reduction in 28-day partial-onset seizure frequency over placebo. Levetiracetam was a concomitant medication in approximately 20% of the patients in two of the studies, and brivaracetam provided no added benefit in these patients. Brivaracetam and levetiracetam have not been directly compared in clinical studies.

Indications for levetiracetam include not only patients with partial-onset seizures but also patients with myoclonic seizures and primary generalized tonic–clonic seizures. However, these are not labeled indications for brivaracetam at present.

Adverse events reported most often in the clinical studies of brivaracetam included somnolence/sedation (16%), dizziness (12%), fatigue (9%), and nausea/vomiting (5%). Risk of sedation and other neurological adverse events is greatest early in treatment but can occur at any time. Patients should be cautioned not to drive or operate machinery until they have gained sufficient experience with the medication to determine whether it adversely affects their ability to participate in these activities. Concurrent use of other central nervous system depressants, including alcoholic beverages, should be expected to increase the likelihood of neurological adverse events.

There have been infrequent reports of hypersensitivity reactions (e.g., bronchospasm, angioedema) in patients treated with brivaracetam, and the drug should be discontinued if such events occur. Its use is contraindicated in patients known to be hypersensitive to the drug or to any of the inactive ingredients in the formulation.

AEDs, including brivaracetam, increase the risk of suicidal thoughts or behavior. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Psychiatric adverse events, including psychotic symptoms (e.g., hallucinations, paranoia) and nonpsychotic symptoms (e.g., anxiety, irritability, mood swings), have been experienced by some patients. A total of 1.7% of patients treated with brivaracetam discontinued treatment because of psychiatric reactions, compared with 1.3% of patients who received placebo.

Brivaracetam is included in Schedule V under the provisions of the Controlled Substances Act, whereas levetiracetam is not a controlled substance. In the recommended dosage, brivaracetam caused fewer sedative and euphoric effects than alprazolam (a Schedule IV drug). However, with higher doses, the new drug was similar to alprazolam on other measures of abuse.

Brivaracetam is classified in Pregnancy Category C and should be used during pregnancy only if the anticipated benefit justifies fetal risk. It is not known whether the drug is excreted in human milk, and a decision should be made whether to discontinue breastfeeding or not use the drug. Its effectiveness and safety in patients younger than 16 years of age have not been established. For treatment of patients with partial-onset seizures, levetiracetam is indicated for patients as young as 1 month of age.

Following oral administration, brivaracetam is almost completely absorbed, and the tablets, oral solution, and injection formulations can be used interchangeably. It is metabolized primarily by hydrolysis and secondarily by a hydroxylation pathway that is mediated primarily by CYP2C19. Patients who are CYP2C19 poor metabolizers, or who are taking a CYP2C19 inhibitor concurrently, may require a dosage reduction. More than 95% of a dose of the new drug is excreted in the urine, almost entirely in the form of metabolites. Exposure of brivaracetam is increased in patients with hepatic impairment, and a dosage reduction is recommended for patients with all stages of hepatic impairment. Dosage adjustment of dosage is not necessary in patients with renal impairment. However, data are not available for patients with end-stage renal disease who are undergoing dialysis, and use of brivaracetam is not recommended in these patients.

Concurrent use of rifampin with brivaracetam reduced plasma concentrations of the new drug by 45%, an effect that is probably the result of CYP2C19 induction. The dosage of brivaracetam should be increased in patients taking the two medications concurrently.

Concomitant use of brivaracetam with numerous other AEDs has also been evaluated for the potential for interactions. None of the possible interactions was of a magnitude requiring a dosage adjustment of brivaracetam. However, the new drug is an inhibitor of epoxide hydrolase, and concurrent use with carbamazepine resulted in increased concentrations of its active metabolite, carbamazepine epoxide. It may be necessary to reduce the dosage of carbamazepine in patients receiving these agents concurrently. Brivaracetam has also been reported to increase plasma concentrations of phenytoin, and patients treated with these agents concomitantly should be closely monitored.

Recommended starting dosage of brivaracetam is 50 mg twice a day. Based on individual patient tolerability and therapeutic response, the dosage may be reduced to 25 mg twice daily or increased to 100 mg twice daily. In patients with a stage of hepatic impairment, the recommended starting dosage is 25 mg twice daily, and the recommended maximum dosage is 75 mg twice daily. When rifampin is used concurrently with brivaracetam, the dosage of the new drug should be increased to up to double of the usual dosage.

When oral administration is not feasible, brivaracetam may be administered intravenously over 2 to 15 minutes at the same dosage and same frequency as with oral administration. The experience with I.V. use of the new drug is limited to 4 consecutive days of treatment.

As with most AEDs, brivaracetam should be withdrawn gradually when treatment is to be discontinued because of the risk of increased seizure frequency and status epilepticus. However, if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.
Brivaracetam tablets are supplied in 10-, 25-, 50-, 75-, and 100-mg strengths and should be swallowed whole with liquid. The oral solution formulation contains the drug in a 10 mg/mL concentration, and dilution is not necessary. This formulation may also be administered intravenously without further dilution or mixed with 0.9% sodium chloride injection, 5% dextrose injection, or lactated ringers injection. The diluted solution should not be stored for more than 4 hours at room temperature.

Comparison of brivaracetam with levetiracetam

Advantages
- Reduced seizure frequency in some patients in whom previous treatments did not provide adequate control

Disadvantages
- Has not been compared directly with other antiepileptic drugs in clinical studies
- Labeled indications more limited (brivaracetam is also indicated for adjunctive treatment of patients with myoclonic seizures and primary generalized tonic–clonic seizures)
- Has not been evaluated in patients younger than 16 years of age (whereas levetiracetam is indicated for younger patients, the age of which is based on indication)
- Administered twice daily (whereas the extended-release formulation of levetiracetam is administered once daily for patients with partial-onset seizures)
- Included in Schedule V (whereas levetiracetam is not a controlled substance)

Antiasthmatic agent: Reslizumab

The symptoms of many patients with asthma are managed effectively with use of a beta-2-adrenergic agonist (e.g., salmeterol), muscarinic antagonist (e.g., tiotropium), and/or a corticosteroid (e.g., fluticasone) administered by oral inhalation. Certain corticosteroids (e.g., prednisone) are sometimes administered orally in patients with more severe symptoms. Even though these regimens are effective in most of the more than 20 million Americans with asthma, many patients do not experience adequate reduction of symptoms and associated complications with conventional therapy, and more than 400,000 asthma-related hospitalizations occur each year.

Multiple cell types, including eosinophils and mediators (e.g., cytokines), are involved in the inflammatory process that occurs in the airways of the lungs. Interleukin-5 (IL-5) is the major cytokine responsible for growth and differentiation, recruitment, activation, and survival of eosinophils. In 2015, mepolizumab (Nucala—GlaxoSmithKline) was approved as the first IL-5 antagonist for add-on maintenance treatment for patients with severe asthma and an eosinophilic phenotype. It is administered subcutaneously and acts by reducing the production and survival of eosinophils.

Reslizumab (Cinqair—Teva), indicated for add-on maintenance treatment of patients with severe asthma and an eosinophilic phenotype, is the second IL-5 antagonist to be approved. Like mepolizumab, it is a monoclonal antibody; unlike its predecessor, it is administered by I.V. infusion and is not indicated in patients younger than 18 years of age, whereas the labeled indications for mepolizumab include patients as young as 12 years of age. Neither reslizumab nor mepolizumab is indicated for treatment of other eosinophilic conditions or for relief of acute bronchospasm or status asthmaticus.

Reslizumab’s effectiveness was demonstrated in four placebo-controlled studies in patients with severe asthma who were being treated with other antiasthmatic medications. Two of the studies continued for 52 weeks, and reslizumab provided a reduction of more than 50% in the rate of asthma exacerbations, including those that required use of a systemic corticosteroid as well as those that required hospitalization or an emergency department visit. Use of reslizumab resulted in a significant improvement in lung function as reflected by increases in forced expiratory volume in 1 second (FEV1) determinations.

Although its properties and indications differ from those of reslizumab and mepolizumab, a third monoclonal antibody, omalizumab (Xolair—Genentech/Novartis), has also been used for treatment of patients with asthma. Omalizumab is administered subcutaneously for treatment of moderate to severe persistent asthma in patients with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with an inhaled corticosteroid. It is also indicated for treatment of chronic idiopathic urticaria in patients who remain symptomatic despite antihistamine treatment. No studies exist that compare the three drugs directly with each other.

The most important risk associated with use of reslizumab is anaphylaxis, which was reported in 0.3% of the patients in the clinical studies and is included in a boxed warning in drug labeling. For this reason, reslizumab should be administered in a health care setting by a health professional who is prepared to manage anaphylaxis. Patients should be observed for an appropriate period of time following I.V. infusion of reslizumab. If severe systemic reactions, including anaphylaxis, occur, administration should be stopped immediately and appropriate medical treatment provided. Reslizumab is contraindicated in patients with known hypersensitivity to the drug or any excipients in its formulation. Although hypersensitivity reactions are also a risk with use of mepolizumab, the strength of the concern does not rise to the level of the boxed warning included in the reslizumab labeling.

Reslizumab was well tolerated in clinical studies, with creatine phosphokinase elevations (14%), oropharyngeal pain (3%), and myalgia (1%), the most commonly experienced adverse events. Malignant neoplasms occurred in a small number of patients (0.6% compared with 0.3% of those in the placebo group). These responses were diverse and not associated with any particular tissue type. However, this risk is identified in the warnings in the reslizumab labeling, whereas it is not included in the mepolizumab labeling.

Use of reslizumab or mepolizumab may permit a reduced...
dosage of corticosteroids that have been part of a patient’s maintenance treatment. Dosage reduction of a corticosteroid may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. Therefore, treatment with a systemic or inhaled corticosteroid should not be discontinued abruptly but on a gradual basis.

Because eosinophils may be involved in the immunological response to some helminth infections, patients with known parasitic infections were excluded from participation in the clinical studies of reslizumab. It is not known whether reslizumab will influence a patient’s response against a parasitic infection, and preexisting helminth infections should be treated before initiating therapy with the new drug. If a helminth infection occurs during treatment with reslizumab and does not respond to antihelminth treatment, reslizumab should be discontinued until the infection resolves.

Information on use of reslizumab in pregnant women is very limited, although there was no evidence of fetal harm in animal studies. The reslizumab labeling notes that its safety and effectiveness in patients younger than 18 years of age have not been established. Although only 39 patients in the clinical studies were in the 12 years to 17 years age range, the asthma exacerbation rate was actually higher in these patients than in those receiving placebo. Therefore, reslizumab is not indicated for use in patients younger than 18 years, whereas the indications for mepolizumab include patients as young as 12 years.

As with other monoclonal antibodies, reslizumab is degraded by enzymatic proteolysis into small peptides and amino acids.

Reslizumab is administered by IV. infusion and should not be used as an I.V. push or bolus. Recommended dosage is 3 mg/kg once every 4 weeks, infused over a period of 20 to 50 minutes.

The injection is supplied in single-use vials containing the drug in a concentration of 100 mg/10 mL. The vials should be stored in a refrigerator. The dose of the drug should be prepared and administered by a health professional. The volume of solution needed to provide the dose of reslizumab should be withdrawn from the vial and added slowly to an infusion bag containing 50 mL of 0.9% sodium chloride injection.

To minimize foaming, neither the vial nor the infusion bag should be withdrawn from the vial and added slowly to an infusion bag containing 50 mL of 0.9% sodium chloride injection.

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To minimize foaming, neither the vial nor the infusion bag should be shaken.

**Psoriasis agent: Ixekizumab**

Psoriasis, a chronic immune-mediated disease that affects an estimated 7.5 million Americans, is characterized by thick and extensive skin lesions (plaques) that can cause itching, scaling, and pain. Mild and limited lesions can often be treated effectively with topically applied medications (e.g., corticosteroids, calcipotriene [a vitamin D analog]). Treatment options for more widespread and/or severe lesions, as well as lesions that have not responded adequately to topical treatment, include phototherapy with ultraviolet light, systemic therapy with an orally administered medication (e.g., methotrexate, apremilast [Otezla—Celgene]) or a parenterally administered medication (e.g., a tumor necrosis factor [TNF] inhibitor such as adalimumab [Humira—AbbVie] or etanercept [Enbrel—Amgen]).

Certain currently occurring interleukins have been identified as having a role in the occurrence and worsening of psoriasis, and the development of interleukin receptor antagonists has been a focus of research efforts. Ustekinumab (Stelara—Janssen Biotech) inhibits interleukins 12 and 23 (IL-12/23) and was the first interleukin antagonist to be approved for treatment of psoriasis. Interleukin-17A (IL-17A) is another interleukin that is present in elevated concentrations in psoriatic plaques, and the IL-17A antagonist secukinumab (Cosentyx—Novartis) was marketed in 2015 for treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. It has also been subsequently approved for treatment of patients with psoriatic arthritis and ankylosing spondylitis.

Like secukinumab, ixekizumab (Taltz—Lilly) is a monoclonal antibody that inhibits IL-17A. Both agents are administered subcutaneously, and ixekizumab was approved in early 2016 for the same indication for which secukinumab was initially approved: treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Izekizumab’s effectiveness was demonstrated in three placebo-controlled studies that included almost 4,000 participants who were candidates for phototherapy or systemic therapy. Forty-nine percent of the patients had received prior conventional systemic therapy, and 26% had received prior biologic therapy. Primary endpoints were a reduction in the Psoriasis Area and Severity Index (PASI) score of at least 75% (PASI 75) from baseline to week 12 and an improvement in the Physician Global Assessment (PGA) to clear or minimal. Between 87% and 90% of the patients treated with ixekizumab attained a PGA of clear, compared with 0% or fewer of those who received placebo. Approximately 70% of those treated with the new drug attained a PASI 90, compared with fewer than 3% of those receiving placebo.

Approximately 40% of the patients treated with ixekizumab received a PGA of clear, compared with 0% of those receiving placebo. In two studies, patients who were responders at week 12 were treated with maintenance doses of ixekizumab every 4 weeks for an additional 48 weeks. Seventy-five percent of the patients who had a clear or mini-

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**Comparison of reslizumab with mepolizumab**

**Advantages**
- Less likely to cause injection site reactions, headache, and back pain

**Disadvantages**
- May be more likely to cause anaphylaxis (boxed warning)
- Malignant neoplasms reported in clinical studies
- Administered intravenously (whereas mepolizumab is administered subcutaneously)
- Less-convenient administration for patients (doses must be prepared and administered by a health professional)
- Not indicated for patients younger than 18 years of age (whereas mepolizumab is indicated for patients as young as 12 years)
mall PGA response at week 12 maintained this response at week 60.

Also in two studies, ixekizumab was compared with etanercept (50 mg/twice/wk). PASI 75 and PASI 90 scores for patients treated with ixekizumab for 12 weeks were 87% and 64%, respectively, compared with 41% and 18%, respectively, for those treated with etanercept.

As with other medications that suppress immune function, ixekizumab increases the risk of infection, with upper respiratory tract infections (14%) one of the most commonly experienced events, although the frequency of this reaction was similar in patients who received placebo (13%). Oral candidiasis, conjunctivitis, and tinea infections also occurred more frequently in patients treated with ixekizumab compared with those in the placebo group. If a serious infection occurs during treatment, the drug should be discontinued and the patient closely monitored until the infection resolves. Patients treated with ixekizumab should not be treated with live vaccines and, before initiating treatment with the new drug, consideration should be given to completing all age-appropriate immunizations.

Patients should be evaluated for tuberculosis infection before initiating treatment with ixekizumab. In patients with a history of latent or active tuberculosis in whom an adequate course of antitubercular therapy cannot be confirmed, such treatment should be considered before initiating treatment with the new drug.

In the clinical studies, there were infrequent reports of Crohn disease (0.1%) and ulcerative colitis (0.2%), including exacerbations. Although these events were reported in only a small number of patients, they occurred more frequently than in those receiving placebo (0%), and patients should be monitored for the onset or exacerbation of inflammatory bowel disease. A small number of patients in the clinical studies experienced serious hypersensitivity reactions, including angioedema and urticaria (each 0.1%). If such an event occurs, the drug should be discontinued immediately.

In addition to upper respiratory tract infections, injection site reactions (17%) have been commonly experienced with use of ixekizumab. Although ixekizumab and secukinumab have not been directly compared in clinical studies, results of studies for the individual drugs suggest that injection site reactions are more likely with ixekizumab. In the studies in which ixekizumab was compared with etanercept, the incidence of injection site reaction was lower with etanercept (11%).

Only limited information is available on use of ixekizumab in pregnant women but, based on results of studies in animals, the drug appears very unlikely to cause teratogenic effects or embryofetal toxicity. Safety and effectiveness of the new drug in patients younger than 18 years of age have not been established.

Following subcutaneous administration, ixekizumab's bioavailability ranged from 60% to 81%. Its metabolism has not been characterized but is thought to be degraded into small peptides and amino acids via catabolic pathways. Clinically important changes in activity in patients with hepatic or renal impairment are not anticipated.

Izekizumab injection is supplied in single-dose prefilled syringes and single-dose prefilled autoinjectors containing 80 mg of the drug in 1mL of solution. The products should be protected from light and stored in a refrigerator. When the drug is to be administered, it should be allowed to reach room temperature for 30 minutes following removal from the refrigerator. The product should not be shaken.

Recommended dosage of ixekizumab is 160 mg (two 80-mg injections) at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks.

**Comparison of ixekizumab with secukinumab**

**Advantages**
- Following initial dose (two injections), dose is administered as a single injection (whereas the recommended dosage of secukinumab for patients with plaque psoriasis requires two injections for each dose)
- Less likely to cause reactions in latex-sensitive individuals
- Labeled indications more limited (labeled indications for secukinumab also include patients with psoriatic arthritis and ankylosing spondylitis)
- May be more likely to cause injection-site reactions

**Hyperkalemia agent: Patiromer sorbitex calcium**

Hyperkalemia, characterized by a serum potassium concentration greater than 5.0 mEq/L (value varies slightly among laboratories), may be associated with complications such as cardiac arrhythmias. It is most often experienced by patients with kidney disease, heart failure, or diabetes, particularly in those who are taking medications that inhibit the renin-angiotensin-aldosterone system (RAAS), such as angiotensin-converting enzyme inhibitors (ACEIs; e.g., lisinopril), angiotensin receptor blockers (ARBs; e.g., valsartan), the direct renin inhibitor aliskiren (Tekturna—Novartis), and aldosterone antagonists (e.g., spironolactone, eplerenone).

Management of hyperkalemia has involved approaches such as reducing the dosage of the causative medication(s), using an alternative medication, reducing potassium intake, and/or increasing excretion with certain diuretics. The cation-exchange resin sodium polystyrene sulfonate (e.g., Kayexalate—Concordia Pharmas) has been used orally or as an enema in treatment of hyperkalemia. However, it may cause serious gastrointestinal adverse events as well as sodium and fluid retention.

Patiromer sorbitex calcium (Veltassa—Relypsa), the first drug to be approved for treatment of hyperkalemia in more than 50 years, consists of the active moiety, patiromer, a non-absorbed potassium-binding polymer, and a calcium–sorbitol counterion. When administered orally, the calcium–sorbitol counterion is exchanged for potassium that binds with patiromer in the lumen of the gastrointestinal tract. This exchange results in reduced potassium absorption and in-
creased fecal potassium excretion, thereby reducing serum potassium concentrations. Because patiromer has a delayed onset of action, it should not be used as an emergency treatment for life-threatening hyperkalemia.

Patiromer’s effectiveness was evaluated in patients with hyperkalemia and chronic kidney disease who were on stable doses of at least one RAAS inhibitor. After 4 weeks of treatment, the mean changes in serum potassium concentration in patients with baseline potassium of 5.1 to less than 5.5 mEq/L or 5.5 to less than 6.5 mEq/L were −0.65 mEq/L and −1.23 mEq/L, respectively. In addition, 76% of patients experienced a reduction in serum potassium concentrations to the target range of 3.8 mEq/L to less than 5.1 mEq/L. In a study of patients who had hyperkalemia, chronic kidney disease, and type 2 diabetes and were on RAAS inhibitor therapy, patiromer’s effectiveness in reducing serum potassium concentrations was maintained during continued therapy for up to 52 weeks. Availability of the new drug provides the opportunity to reduce the risk of hyperkalemia in patients with chronic diseases (e.g., kidney disease, heart failure, diabetes) for whom continued use of a RAAS inhibitor is beneficial notwithstanding the tendency of RAAS inhibitors to increase serum potassium concentrations.

Adverse events most often experienced by patients in clinical studies included constipation (7%), diarrhea (5%), nausea (2%), abdominal discomfort (2%), and flatulence (2%). Use of patiromer should be avoided in patients with severe constipation or bowel obstruction or impaction, including abnormal postoperative bowel motility disorders, because the drug may be ineffective and may worsen gastrointestinal conditions.

Hypokalemia (serum potassium < 3.5 mEq/L) was reported in 5% of the patients. In addition to binding to potassium, patiromer also binds to magnesium in the colon, and approximately 9% of patients in the clinical studies developed hypomagnesemia (serum magnesium < 1.4 mg/dL). Serum magnesium concentrations should be monitored and use of a magnesium supplement considered for patients who experience low magnesium concentrations.

Patiromer binds to many orally administered medications, which may reduce their absorption and effectiveness. This is the subject of a boxed warning in the drug labeling, and other oral medications should be administered at least 6 hours before or 6 hours after patiromer. If it is not possible to separate administration of the medications by at least 6 hours, a decision should be made to administer either patiromer or the other oral medication.

Patiromer is not absorbed and is not expected to present a risk if it is used during pregnancy or by a woman who is breastfeeding. Its effectiveness and safety in pediatric patients have not been established.

Patiromer sorbitex calcium is a powder that is insoluble in water. Each gram of patiromer, the active moiety, is equivalent to a nominal amount of 2 g of patiromer sorbitex calcium. The inactive ingredient is xanthan gum. The medication is packaged in single-use packets containing 8.4 g, 16.8 g, and 25.2 g of patiromer powder for oral suspension. The product should be stored in a refrigerator and should not be heated when it is prepared for administration. If stored at room temperature, it must be used within 3 months of being taken out of the refrigerator.

Patiromer should be administered with food but not added to heated foods or liquids. The recommended starting dosage is 8.4 g once daily. Serum potassium concentrations should be monitored, and the dosage should be adjusted based on the potassium concentration and the desired target range. The dosage may be increased at 1-week or longer intervals, in increments of 8.4 g, up to the maximum dosage of 25.2 g once daily.

Each dose of patiromer should be prepared immediately before administration. The contents of a packet should be emptied into a glass or cup containing about 1 oz of water and stirred thoroughly, and an additional 2 oz of water should be added and thoroughly mixed. The powder does not dissolve, and the mixture is cloudy, and patients should be instructed to drink the mixture immediately. If some powder remains in the glass after drinking, more water should be added and the mixture stirred, with this process repeated as needed until the entire dose is administered.

### Comparison of patiromer sorbitex calcium with sodium polystyrene sulfonate

**Advantages**

- Less risk of serious gastrointestinal adverse events
- Less risk of sodium and fluid retention
- Administered once daily (whereas sodium polystyrene sulfonate is administered multiple times daily in some patients)

**Disadvantages**

- Rectal administration has not been evaluated (whereas sodium polystyrene sulfonate has been administered as an enema when oral administration is not feasible)
- Should be refrigerated
CPE NEW THERAPEUTIC AGENTS MARKETED IN 2016: PART 1

CPE assessment
This assessment must be taken online; please see “CPE information” in the sidebar below 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 use pairings is correct?
   a. Pimavanserin: depression
   b. Brivaracetam: psoriasis
   c. Patiromer: hyperkalemia
   d. Ixekizumab: asthma

2. Which of the following drug: mechanism-of-action pairings is correct?
   a. Reslizumab: interleukin-17A antagonist
   b. Velpatasvir: HCV NS5A inhibitor
   c. Elbasvir: HCV NS3/4A protease inhibitor
   d. Patiromer: tumor necrosis factor blocker

3. Which of the following agents is administered subcutaneously?
   a. Ixekizumab
   b. Reslizumab
   c. Brivaracetam
   d. Pimavanserin

4. Which of the following agents is administered twice daily?
   a. Elbasvir/grazoprevir
   b. Velpatasvir/sofosbuvir
   c. Pimavanserin
   d. Brivaracetam

5. With use of which of the following agents is prolongation of the QT interval an important concern?
   a. Patiromer
   b. Pimavanserin
   c. Elbasvir/grazoprevir
   d. Reslizumab

6. With use of which of the following agents is hypomagnesemia most likely to occur?
   a. Velpatasvir/sofosbuvir
   b. Ixekizumab
   c. Patiromer
   d. Brivaracetam

7. Which of the following agents should not be administered if a patient has an active helminth infection?
   a. Reslizumab
   b. Pimavanserin
   c. Patiromer
   d. Brivaracetam

8. With which of the following agents is concurrent use of a proton pump inhibitor not recommended?
   a. Reslizumab
   b. Pimavanserin
   c. Brivaracetam
   d. Velpatasvir/sofosbuvir

9. Which of the following statements is correct about elbasvir/grazoprevir?
   a. It is the first regimen to be approved for treatment of HCV infection of all six major genotypes.
   b. It is the first regimen for treatment of HCV infection that does not include ribavirin.
   c. Hepatic laboratory testing should be performed during treatment.
   d. Diarrhea is the adverse event most often associated with its use.

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, 2019, 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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2. Enter the title of this article or the ACPE number to search for the article and click on the title of the article to start the home study.
3. To receive CPE credit, select Enroll Now or Add to Cart from the left navigation and successfully complete the assessment (with randomized questions) and evaluation.
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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.
10. Which of the following statements is correct about elbasvir/grazoprevir?
   a. It should be administered with a meal having a high fat content.
   b. Concurrent use with a strong CYP3A inducer is contraindicated.
   c. Concurrent use with rosuvastatin is contraindicated.
   d. The dosage should be doubled in patients with HCV and HIV-1 coinfection.

11. Which of the following statements is correct about velpatasvir/sofosbuvir?
   a. It must be used in combination with ribavirin in patients with HCV genotypes 2 and 3 infection.
   b. Patients with HCV genotype 1a infection should be tested for NS5A resistance--associated polymorphisms.
   c. It is the first regimen for treatment of HCV infection for which use of ribavirin is not recommended.
   d. Concurrent use with amiodarone is not recommended because of an increased risk of bradycardia.

12. Which of the following statements is correct about velpatasvir/sofosbuvir?
   a. Dosage adjustment is not necessary in patients with hepatic impairment.
   b. Its action may be increased by concurrent use of a strong CYP3A inducer.
   c. It is administered three times daily.
   d. Treatment duration is 8 weeks in patients who do not have cirrhosis.

13. Which of the following statements is correct regarding pimavanserin?
   a. It acts as a dopamine D2 receptor antagonist.
   b. It is indicated for treatment of patients with dementia-related psychosis.
   c. Concurrent use with levodopa should be avoided.
   d. It is metabolized to a major active metabolite.

14. Which of the following statements is correct about pimavanserin?
   a. It should not be used concurrently with antiarrhythmic agents such as amiodarone and quinidine.
   b. It must be administered apart from food.
   c. It may be used in patients with hepatic impairment without adjustment of the dosage.
   d. Dosage should be increased in patients who are also being treated with a strong CYP3A4 inhibitor.

15. Which of the following statements is correct about brivaracetam?
   a. It should be used in combination with levetiracetam.
   b. It is classified as an interleukin receptor antagonist.
   c. Somnolence and sedation are the most common adverse events associated with its use.
   d. It is classified in Schedule IV.

16. Which of the following statements is correct about brivaracetam?
   a. It is excreted in unchanged form in the urine.
   b. Dosage should be reduced in patients with hepatic impairment.
   c. It is indicated for use in adults and in children as young as 1 month of age.
   d. It is supplied in tablets for oral use and in vials for subcutaneous administration.

17. Which of the following statements is correct about reslizumab?
   a. Its properties and use are most similar to those of mepolizumab.
   b. It is indicated for treatment of patients with asthma that is attributed to an allergic response.
   c. It is indicated for use in both adults and children.
   d. Its labeling includes a boxed warning on the risk of renal toxicity.

18. Which of the following statements is correct about ixekizumab?
   a. It is an inhibitor of interleukins 12 and 23.
   b. Its properties and use are most similar to those of vedolizumab.
   c. In clinical trials, it was considered similar in effectiveness to etanercept.
   d. Patients should be evaluated for tuberculosis before initiating treatment.

19. Which of the following statements is correct about ixekizumab?
   a. It should be administered apart from food.
   b. It is administered every 2 weeks for the first 12 weeks and then every 4 weeks thereafter.
   c. Dosage should be reduced in patients with impaired renal function.
   d. It should not be used concurrently with a strong CYP3A4 inhibitor.

20. Which of the following statements is correct about patiromer sorbitex calcium?
   a. Concurrent use with an ACE inhibitor must be avoided.
   b. Sedation and fatigue are the adverse events most often associated with its use.
   c. It should be administered at least 6 hours apart from other oral medications.
   d. It should be administered apart from food.