**Abstract**

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

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

**Data synthesis:** This review covers eight new therapeutic agents marketed in the United States in 2015: ivabradine, cangrelor, deoxycholic acid, filgrastim-sndz, cholic acid, eluxadoline, parathyroid hormone, and lumacaftor-ivacaftor. Indications and information on dosage and administration for these agents are reviewed, as are the most important pharmacokinetic properties, drug interactions, and other precautions. Practical considerations for the use of these new agents also are discussed. Whenever possible, properties of the new drugs are compared with those of older agents marketed for the same indications.

**Summary:** Ivabradine is a new first-in-class I(f) channel inhibitor approved to reduce hospitalization from worsening heart failure. Cangrelor is an antiplatelet P2Y<sub>12</sub> inhibitor indicated to reduce the risk of thrombotic events in patients undergoing percutaneous coronary intervention procedures. Deoxycholic acid is the first cytolytic drug approved to reduce submental fat (fat below the chin). Filgrastim-sndz is the first biosimilar approved by FDA in the United States. Cholic acid is a synthetic bile acid indicated to treat patients with bile acid synthesis disorders. Eluxadoline is a mu opioid receptor agonist approved for the treatment of diarrhea-predominate irritable bowel syndrome. Recombinant parathyroid hormone is approved as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. Lumacaftor/ivacaftor is a fixed-dose combination drug for cystic fibrosis patients with the F508del mutation. The combination contains a cystic fibrosis transmembrane conductance regulator (CFTR) corrector and CFTR potentiator.

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

1. Which of the following drugs is administered subcutaneously?
   a. Cangrelor  c. Parathyroid hormone
   b. Cholic acid  d. Ivabradine

2. Bleeding is the most serious concern with which of the following agents?
   a. Cangrelor  c. Eluxadoline
   b. Ivabradine  d. Lumacaftor/ivacaftor

3. Which of the following statements is correct about ivabradine?
   a. Ivabradine should be taken on an empty stomach.
   b. Ivabradine is safe in pregnancy.
   c. Ivabradine is contraindicated if a patient’s blood pressure is less than 90/50 mm Hg.
   d. Ivabradine should not be used in conjunction with beta blockers.

Objective
In the second part of this four-part series on new therapeutic agents marketed in the United States in 2015, eight new therapeutic agents are covered: ivabradine, cangrelor, deoxycholic acid, filgrastim-sndz, cholic acid, eluxadoline, parathyroid hormone, and lumacaftor/ivacaftor.

New cardiology agents
According to the American Heart Association, heart failure is a common condition affecting approximately 5.1 million people in the United States. One-half of those who develop heart failure die within 5 years of diagnosis. In 2009, one in nine deaths included heart failure as a contributing cause. Risk factors for developing heart failure include presence of coronary artery disease; hypertension; diabetes; smoking; eating foods high in fat, cholesterol, and sodium; physical inactivity; and obesity.

Ivabradine
Ivabradine (Corlanor—Amgen) is a new first-in-class If() channel inhibitor approved to reduce hospitalization from worsening heart failure. It is indicated for use in patients with chronic symptomatic heart failure with a left ventricular ejection fraction (LVEF) of 35% or less and in sinus rhythm with a resting heart rate of 70 beats or greater per minute who are maximized on beta-blocker therapy or have a contraindication to beta-blocker use.

Ivabradine has a novel mechanism of action. It blocks the hyperpolarization-activated, cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker If() current, which regulates heart rate. Food delays absorption by approximately 1 hour and increases plasma concentrations. Ivabradine should be taken with meals. The drug is 70% protein bound.

The starting dose of ivabradine is 5 mg twice daily; however, patients with conduction defects should initiate dosing at 2.5 mg twice daily. After 2 weeks of therapy, the dose should be adjusted according to heart rate. See Table 2 for additional details for dosing of ivabradine.

Efficacy of ivabradine was evaluated in two large, randomized, double-blind, placebo-controlled trials. The SHIFT trial randomized 6,558 patients with coronary disease and left ventricular dysfunction to ivabradine or placebo. Patients had LVEF of less than 35% and an elevated initial heart rate of greater than 70 beats per minute, and had been admitted to the hospital for treatment of heart failure within the previous year. In addition, patients had to be clinically stable on maximally tolerated doses of beta blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), spironolactone, and diuretics. The primary endpoint was a composite of the first occurrence of either hospitalization for worsening heart failure or cardiovascular death.

Results of SHIFT showed a statistically significant 2% reduction over 2 years in all-cause hospitalizations (1,356 vs. 1,231) in the ivabradine group compared with placebo, but there was no significant difference in all-cause mortality. In the overall treatment population, ivabradine had no statistically significant benefit on cardiovascular death.

The BEAUTIFUL trial enrolled more than 10,000 patients in sinus rhythm with stable coronary artery disease. Patients differed from SHIFT in that they were included with a heart rate of greater than 60 beats per minute and an LVEF of less than 40%. Patients had to be stable on a conventional heart failure regimen (e.g., beta blockers, ACEs or ARBs). Results showed an average heart rate reduction of 6 beats per minute from the baseline rate of 71.9 ± 9.9 beats per minute.

No significant effects were found for the primary endpoints of cardiovascular death or hospitalization resulting from either heart failure or acute myocardial infarction (MI). Both SHIFT and BEAUTIFUL showed that many patients with heart failure are not being treated with optimal doses of beta blockers.

Contraindications are lengthy and are listed below.
- Acute decompensated heart failure
- Blood pressure less than 90/50 mm Hg
- Sick sinus syndrome, sinoatrial block, or third-degree atrioventricular (AV) block, unless a functioning demand pacemaker is present
- Resting heart rate of less than 60 bpm prior to treatment
- Severe hepatic impairment
- Dependence on a pacemaker

Warnings and precautions include the need to monitor patients for atrial fibrillation, heart rate decreases, and bradycardia symptoms during treatment. In addition, ivabradine is not recommended in patients with second-degree AV block.

Adverse effects associated with the drug include bradycardia, hypertension, and atrial fibrillation. Ivabradine may also cause an adverse effect known as luminous phenomena. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field. Approximately 1 hour and increases plasma concentrations.
CPE  New Therapeutic Agents Marketed in 2015: Part 2

Cangrelor

Cangrelor (Kengreal—The Medicines Company) is an I.V. antiplatelet agent indicated as an adjunct to percutaneous coronary intervention (PCI) for reducing the risk of peri-procedural MI, repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a P2Y\textsubscript{12} platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.\textsuperscript{5}

In an analysis of hospital discharge data from 2010, CDC has estimated that PCI is performed on approximately 500,000 people in the United States annually.\textsuperscript{6} PCI is commonly referred to as angioplasty, and more often than not, a stent is placed during PCI to help maintain patency of vessels. Risks during PCI include MI, repeat coronary revascularization, and ST.

Cangrelor, similar to ticagrelor, works by binding selectively and reversibly to the P2Y\textsubscript{12} receptor on platelets to prevent platelet activation and aggregation. Other P2Y\textsubscript{12} inhibitors (i.e., prasugrel, clopidogrel, and ticlopidine) bind irreversibly to the receptor (Table 5). There appears to be little clinical relevance regarding how antiplatelets bind to the P2Y\textsubscript{12} receptor. No antidote is available, and an infusion of platelets is required to return bleeding time to normal.

Cangrelor exhibits linear pharmacokinetics and is rapidly distributed and metabolized. Patients reach a maximum concentration within 2 minutes after I.V. bolus administration. Metabolism is independent of hepatic function and does not interfere with other drugs metabolized by the liver. The average elimination half-life is about 3 to 6 minutes. No dose adjustment is necessary for sex, age, and renal or hepatic function.\textsuperscript{5}

Table 1. New therapeutic drugs approved in 2015: Part 2

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>Route</th>
<th>Pronunciation</th>
<th>FDA approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiology</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Corlanor</td>
<td>Amgen</td>
<td>Chronic heart failure</td>
<td>Oral</td>
<td>Eye VAB ra deen</td>
<td>April 2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Adjunct to percutaneous coronary intervention for reducing the risk of periprocedural myocardial infarction, repeat coronary revascularization, and stent thrombosis</td>
<td>I.V.</td>
<td>KAN grel or</td>
<td>June 2015</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>Kengreal</td>
<td>The Medicines Company</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatology</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deoxycholic acid</td>
<td>Kybella</td>
<td>Kythera Biopharm</td>
<td>Excess subcutaneous fat of submental region</td>
<td>SubQ</td>
<td>Dee ox i KOE lik AS id</td>
<td>April 2015</td>
</tr>
<tr>
<td>Hematology/Oncology</td>
<td>Zarfio</td>
<td>Sandoz</td>
<td>Neutropenia</td>
<td>SubQ</td>
<td>fil GRA stim</td>
<td>March 2015</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>Cholbam</td>
<td>Asklepios</td>
<td>Bile acid synthesis disorders</td>
<td>Oral; twice daily</td>
<td>KOE lik AS id</td>
<td>March 2015</td>
</tr>
<tr>
<td></td>
<td>Viberzi</td>
<td>Forest</td>
<td>IBS-D</td>
<td>Oral; twice daily</td>
<td>KOE lik AS id</td>
<td>March 2015</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>Natpara</td>
<td>NPS</td>
<td>Adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism</td>
<td>SubQ</td>
<td>par a THYE roid HOR mone</td>
<td>Jan 2015</td>
</tr>
<tr>
<td>Pulmonology</td>
<td>Orkambi</td>
<td>Vertex</td>
<td>Combination product for treating certain types of cystic fibrosis</td>
<td>Oral</td>
<td>loo ma KAF tor/ eye va KAF tor</td>
<td>July 2015</td>
</tr>
</tbody>
</table>

Abbreviation used: SubQ, subcutaneously; IBS-D, irritable bowel syndrome with diarrhea.

Sources: Refs. 4, 5, 8, 11, 18, 23, 32, 36.
Table 2. Dosing of newly approved therapeutic agents

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Dosage forms</th>
<th>Dosing</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine</td>
<td>Corlanor</td>
<td>5-mg, 7.5-mg oral tablets</td>
<td>5 mg twice daily or 2.5 mg twice daily with meals in patients with a history of conduction defects or who may experience hemodynamic compromise due to bradycardia</td>
<td>Adjust dose according to resting heart rate and tolerability. Maximum dose: 7.5 mg twice daily.</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>Kengreal</td>
<td>Single-use 50-mg/10-mL vial</td>
<td>30 mcg/kg I.V. bolus followed immediately by a 4-mcg/kg/min I.V. infusion</td>
<td>Initiate the bolus infusion prior to PCI. The maintenance infusion should ordinarily be continued for at least 2 hours or for the duration of PCI, whichever is longer.</td>
</tr>
<tr>
<td>Deoxycholic acid</td>
<td>Kybella</td>
<td>SubQ</td>
<td>0.2 mL injected SubQ into submental area; injections spaced 2 cm apart</td>
<td>Maximum of 50 injections or 10 mL. Provides dose of 2mg/cm². May repeat treatment up to six times at intervals no less than 1 month apart.</td>
</tr>
<tr>
<td>Filgrastim-sndz</td>
<td>Zarxio</td>
<td>300-mcg, 480-mcg prefilled syringe</td>
<td>5–10 mcg/kg once daily SubQ based on the indication</td>
<td>Weight-based dosing.</td>
</tr>
<tr>
<td>Cholic acid</td>
<td>Cholbam</td>
<td>50-mg, 250-mg oral capsules</td>
<td>Children and adults: 10–15 mg/kg orally once daily or in two divided doses with food. Concomitant familial hypertriglyceridemia dose: 11–17 mg/kg once daily or in two divided doses</td>
<td>Monitor liver function tests closely. Discontinue if liver function does not improve within 3 months or if complete biliary obstruction occurs.</td>
</tr>
<tr>
<td>Eluxadoline</td>
<td>Viberzi</td>
<td>75-mg, 100-mg oral tablets</td>
<td>100 mg twice daily with food</td>
<td>75 mg twice daily for patients with any of the following conditions: do not have a gallbladder, are unable to tolerate 100 mg, are receiving concomitant OATP1B1 inhibitors, or have mild or moderate hepatic impairment</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>Natpara</td>
<td>25-mcg, 50-mcg, 75-mcg, 100-mcg SubQ</td>
<td>50 mcg once daily</td>
<td>Increase in increments of 25 mcg once daily every 4 weeks; maximum daily dose is 100 mcg.</td>
</tr>
<tr>
<td>Lumacazzor/ivacazzor</td>
<td>Orkambi</td>
<td>200-mg/125-mg oral tablet</td>
<td>400-mg lumacazzor/250-mg ivacazzor (two tablets) every 12 hours</td>
<td>If a dose is missed ≤6 hours from the usual time it is taken, take as soon as possible; otherwise, skip the missed dose and resume the normal dosing schedule.</td>
</tr>
</tbody>
</table>

Abbreviations used: PCI, percutaneous coronary intervention; SubQ, subcutaneously.
Sources: Refs. 4, 5, 8, 11, 18, 23, 32, 36.

Cangrelor should be administered as an I.V. bolus via a dedicated I.V. line prior to PCI, followed by a maintenance infusion (see Table 2 for detailed dosing). Once the maintenance infusion is discontinued, an oral antiplatelet should be administered immediately, since the antiplatelet effect of cangrelor ceases after 1 hour.\(^5\)

Approval of cangrelor was based on results from the CHAMPION PHOENIX trial, which was designed to test whether faster platelet inhibition with cangrelor administered during PCI would reduce the rate of thrombotic events during the procedure, compared with clopidogrel. This trial was a randomized, double-blind study of 11,145 patients with coronary artery disease, including stable angina, unstable angina, non-ST segment elevation MI, and ST segment elevation MI. Patients received standard therapy with aspirin and heparin or bivalirudin and were randomized 1:1 to cangrelor or to clopidogrel. Patients who had already taken an oral P2Y\(_\text{12}\) inhibitor or a glycoprotein IIb/IIIa inhibitor were excluded. The primary efficacy endpoint was a composite of death, MI, ischemia-driven revascularization, and ST within 48 hours after randomization.\(^7\) The primary safety endpoint was severe bleeding at 48 hours.

Cangrelor significantly reduced the occurrence of MI and the need for further revascularization. ST developed in 0.8% of patients in the cangrelor arm and in 1.4% of patients in the clopidogrel arm. Overall, rates of serious bleeding were low but more common in patients treated with cangrelor. Cangrelor did not reduce the risk of death.\(^7\)

Contraindications to cangrelor include significant active bleeding and hypersensitivity issues. As with other FDA-approved antiplatelet drugs, bleeding is the most common adverse reaction. In CHAMPION PHOENIX, bleeding events were more common with cangrelor compared with clopidogrel, regardless of severity. Approximately 1 in every 170 cangrelor patients had a serious bleed, compared with approximately 1 in every 275 clopidogrel patients. Drugs that inhibit platelet function increase the risk of bleeding and should not be coadministered with cangrelor. Clopidogrel,
Deoxycholic acid is extensively bound (98%) to plasma proteins. Endogenous deoxycholic acid is a product of cholesterol metabolism and is excreted intact in feces. Deoxycholic acid is not metabolized to any significant extent under normal conditions. Approval of deoxycholic acid was based on two identical randomized, double-blind, placebo-controlled trials. Patients (n = 1,022) with the appearance of convexity or fullness associated with submental fat were randomized to receive up to six treatments with deoxycholic acid or placebo at no less than 1-month intervals. Included patients were healthy adults (aged 19–65 years, body mass index [BMI] ≤ 40 kg/m²) with moderate or severe convexity or fullness associated with submental fat (i.e., grade 2 or 3 on 5-point grading scales, where 0 = none and 4 = extreme). Fifty-nine percent of patients received all six treatments.9,10

The average age of patients in the studies was 49 years, and the mean BMI was 29 kg/m². Most patients were women (85%) and Caucasian (87%). Upon initiation, 51% of the patients had a clinician-rated submental fat severity rating of moderate, and 49% had a severe rating. Results showed that reductions in submental fat were observed more frequently in participants who received deoxycholic acid, compared with those on placebo. Patients also reported an increase in satisfaction on a six-question survey when asked about the treatment in relation to the amount of their submental fat.9,10

Deoxycholic acid is contraindicated in the presence of infection at the injection sites. Several warnings and precautions exist. Marginal mandibular nerve injury may occur with incorrect injection
Table 4. New therapeutic agents and pregnancy

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Pregnancy category</th>
<th>Comments</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivabradine</td>
<td>Fetal toxicity</td>
<td>Warnings and precautions: Females should use effective contraception.</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>C</td>
<td>No adequate or well-controlled studies in pregnant women</td>
<td>Caution; unknown if excreted in human milk</td>
</tr>
<tr>
<td>Deoxycholic acid</td>
<td>–</td>
<td>No adequate or well-controlled studies in pregnant women</td>
<td>Not studied</td>
</tr>
<tr>
<td>Filgrastim-sndz</td>
<td>C</td>
<td>No adequate or well-controlled studies in pregnant women</td>
<td>Caution; unknown if excreted in human milk</td>
</tr>
<tr>
<td>Cholic acid</td>
<td>–</td>
<td>No studies in animals or humans. Pregnancy exposure registry exists.</td>
<td>Endogenous cholic acid is present in human milk. Not studied.</td>
</tr>
<tr>
<td>Eluxadoline</td>
<td>–</td>
<td>Adverse events were not observed in animal studies.</td>
<td>Unknown if excreted in human milk</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>C</td>
<td>Adverse events were observed in animal studies.</td>
<td>Not recommended; unknown if excreted in human milk</td>
</tr>
<tr>
<td>Lumacaftor/ivacaftor</td>
<td>B</td>
<td>Adverse events were not observed in animal studies.</td>
<td>Caution; unknown if excreted in human milk</td>
</tr>
</tbody>
</table>

Sources: Refs. 4, 5, 8, 11, 18, 23, 32, 36.

Table 5. Comparison of antiplatelet P2Y₁₂ inhibitors

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Route of administration</th>
<th>Mechanism of action</th>
<th>Class</th>
<th>Generic availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticlopidine</td>
<td>Ticlid</td>
<td>Oral</td>
<td>Irreversibly binds to P2Y₁₂ receptor blocking ADP, thereby reducing platelet aggregation</td>
<td>First-generation thienopyridine</td>
<td>Yes</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Plavix</td>
<td>Oral</td>
<td>Irreversibly binds to P2Y₁₂ receptor blocking ADP, thereby reducing platelet aggregation</td>
<td>Second-generation thienopyridine</td>
<td>Yes</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Effient</td>
<td>Oral</td>
<td>Reversibly binds to P2Y₁₂ receptor blocking ADP, thereby reducing platelet aggregation</td>
<td>Third-generation thienopyridine</td>
<td>No</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Brilipta</td>
<td>Oral</td>
<td></td>
<td>Cyclopentyltriazolopyrimidine</td>
<td>No</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>Kengreal</td>
<td>I.V.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation used: ADP, adenosine diphosphate.
Source: Ref. 5.

New hematology/oncology agent: Filgrastim-sndz

Filgrastim-sndz, marketed under the trade name Zarxio (Sandoz), is the first FDA-approved biosimilar in the United States. Zarxio was approved under the first application using the 351(k) biosimilar pathway, which was part of the Biologics Price Competition and Innovation Act of 2009 defined by the Affordable Care Act in 2010. Figure 1 provides an overview of the FDA drug and biologic approval pathways. Filgrastim has been available for some time; it was first FDA approved in 1991. Zarxio is included in this review to educate on the biosimilar pathway.

Biosimilars have been approved for use in Europe for nearly 10 years. In 2004, the European Commission passed legislation creating a biosimilars approval pathway; shortly thereafter, the European Medicines Agency (EMA) released its first set of biosimilar guidelines. In 2006, EMA approved its first biosimilar, and to date, 14 biosimilars have been authorized. Teva obtained market authorization for tbo-filgrastim (Granix) in Europe in 2008, and Sandoz has marketed Zarxio in Europe since 2009.

EMA regulations ensure that (1) biosimilars share the same international nonproprietary name as its reference, (2) each biosimilar has a unique trade name or the name of the technique. Detailed instructions on proper technique are outlined in the product label. Use of deoxycholic acid may lead to dysphagia. Patients with preexisting dysphagia may exacerbate the condition. Hematoma and bruising occur frequently after administration. Use with caution in patients who are being treated with antiplatelet or anticoagulant therapy or in patients who have coagulation abnormalities. Injection in proximity to vulnerable anatomic structures should be avoided because of the increased risk of tissue damage. Caution should also be used in patients who have had prior surgical or aesthetic treatment of the submental area.

As evidenced by the warnings and precautions, injection site edema and swelling, hematoma, pain, numbness, erythema, and induration are the most common adverse reactions occurring in more than 20% of study participants. Deoxycholic acid has no clinically relevant drug interactions. No dosage adjustment is necessary in patients with hepatic impairment. Gender had no impact on pharmacokinetics, and no effects on fertility were seen in animal studies.

Of note, the drug is being distributed in packaging that has a unique hologram on the vial label. If no hologram exists, the product should not be used. In addition, it is being provided in single patient-use vials and should not be diluted or mixed with any other compounds.

Sources: Refs. 4, 5, 8, 11, 18, 23, 32, 36.

New therapeutic agents marketed in 2015: part 2
active substance with the company name, and (3) automatic substitution of the trade name drug for its biosimilar is regulated by each member state in the European Union. FDA intends to issue draft guidance on biosimilar naming in the latter part of 2015.

### Table 6. Comparison of filgrastim products

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Indications</th>
<th>Approval pathway, date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>Neupogen</td>
<td>Amgen</td>
<td>• Prevention of chemotherapy-induced neutropenia</td>
<td>351(a), February 1991</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients with acute myeloid leukemia following induction or consolidation chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Bone marrow transplantation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Peripheral blood progenitor cell collection and therapy</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Severe chronic neutropenia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Acute hematopoietic radiation injury syndrome</td>
<td></td>
</tr>
<tr>
<td>Filgrastim-sndz</td>
<td>Zarxio</td>
<td>Sandoz</td>
<td>• Prevention of chemotherapy-induced neutropenia</td>
<td>351(k), March 2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients with acute myeloid leukemia following induction or consolidation chemotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Bone marrow transplantation</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Peripheral blood progenitor cell collection and therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Severe chronic neutropenia</td>
<td></td>
</tr>
<tr>
<td>Tbo-filgrastim</td>
<td>Granix</td>
<td>Teva</td>
<td>• Decrease the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy associated with a clinically significant incidence of neutropenic fever</td>
<td>351(a), August 2012</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Neulasta</td>
<td>Amgen</td>
<td>• Prevention of chemotherapy-induced neutropenia</td>
<td>351(a), January 2002</td>
</tr>
</tbody>
</table>

*Sources: Refs. 18, 40–42.*

### Figure 1. FDA drug and biologic approval pathways

Abbreviations used: NDA, new drug application; ANDA, abbreviated new drug application; BLA, biologics license application.

Source: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation

Requirements for biosimilarity are detailed by FDA and state that the product may be compared to only one approved biologic. To be deemed “highly similar,” the agent must:
- Share the same physiochemical and functional structure
- Share the same pharmacodynamics, toxicity, toxicoki-
netic, and local tolerance
- Have the same mechanism of action
- Have the same conditions of use (FDA-approved indications)
- Provide the same route of administration, dosage form, and strength

Zarxio is biosimilar to but not interchangeable with Neupogen. Sandoz, the manufacturer, requested a determination of biosimilarity and not interchangeability; therefore, FDA did not evaluate whether Zarxio satisfied the additional standard for interchangeability. According to FDA, “Interchangeable products are both biosimilar to an FDA-approved reference product and can be expected to produce the same clinical result as the reference product in any given patient. An interchangeable product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.”

As part of its stepwise approach to demonstrate biosimilarity, Sandoz completed a head-to-head trial with Neupogen. PIONEER was a randomized, double-blind, parallel-group study in patients with histologically proven breast cancer. Patients eligible for chemotherapy were treated with myelosuppressive TAC (dactinomycin, doxorubicin, and cyclophosphamide), all given via IV. on day 1 of each of six 21-day cycles. The primary endpoint was the duration of severe neutropenia (DSN) in cycle 1 and analysis conducted in the per-protocol population. Results showed no clinically meaningful difference in the primary endpoint between Zarxio and Neupogen. The mean DSN in cycle 1 was 1.17 days for Zarxio and 1.20 days for Neupogen.

Overall, Sandoz has presented data on Zarxio’s biosimilarity to Neupogen for five of six indications: myelosuppressive chemotherapy, acute myeloid leukemia, bone marrow transplantation, autologous peripheral blood progenitor cell collection and therapy, and for severe chronic neutropenia (Table 6). Zarxio appears to show no difference in efficacy, safety, and tolerability when compared with Neupogen and has the same contraindications, warnings, and precautions as those of Neupogen. Common adverse effects are similar as well.

Other available granulocyte–colony stimulating factors (GCSFs) include Neupogen (Amgen), Granix (Teva), and Neulasta (Amgen). Table 6 compares the available GCSFs.

New gastroenterology agents

Cholic acid
Cholic acid (Cholbam—Asklepion Pharmaceuticals) is a bile acid that FDA approved to treat bile acid synthesis disorders (BASDs) resulting from single enzyme defects. It is also approved as an adjunctive treatment of peroxisomal disorders, including Zellweger spectrum disorders. Patients with these rare, genetic, metabolic conditions exhibit manifestations of liver disease, steatorrhea, and complications from decreased fat-soluble vitamin absorption. This is the first approved treatment of its kind for these patients. Cholic acid is approved as an oral treatment for adults and children aged 3 weeks and older.

BASDs can be classified as primary or secondary. Primary disorders result from congenital deficiencies in enzymes, such as cholic acid. Zellweger syndrome, although involved in bile acid synthesis, is considered a secondary disorder and is further classified as a peroxisomal disorder. In healthy patients, endogenous cholic acid is produced in the liver from cholesterol. Those with BASDs lack the enzymes necessary to synthesize cholic acid. The lack of cholic acid results in reduced bile flow, cholestasis, and malabsorption of fats and fat-soluble vitamins in the diet. Signs and symptoms of BASDs include jaundice, failure to thrive, growth deficiency, diarrhea, and steatorrhea. Progressive neurological disease has also been described. In addition, organomegaly, including hepatomegaly and/or splenomegaly, may be seen in bile acid disorders.

The mechanism of action of cholic acid is unclear. Endogenous cholic acid binds to the farnesoid X receptor (FXR). When activated by bile acids, FXR is involved in regulation of bile acid synthesis, conjugation, and transport. It is also involved in various aspects of glucose and lipid metabolism.

Endogenous bile acids, including cholic acid, enhance bile flow and provide the physiologic feedback inhibition of bile acid synthesis.

Cholic acid is absorbed by passive diffusion along the gastrointestinal tract and metabolized in the liver, and conjugated cholic acid is secreted into bile. Patients with concomitant familial hypertriglyceridemia may have poor absorption. After reabsorption in the ileum, it enters another cycle of enterohepatic circulation. Excretion is primarily in the feces.

Cholic acid dosing is weight based, given once daily or in two divided doses. A higher dose is recommended in patients with familial hypertriglyceridemia resulting from poor absorption. See Table 2 for detailed dosing. No dosage adjustments are necessary in renal impairment, and pediatric patients use the same adult weight-based dosing.

Because of the rarity of BASDs, efficacy of cholic acid was established in a small number of patients. One study was a nonrandomized, open-label, single-arm trial in 50 patients over an 18-year period. The second trial was an extension trial of the first study, which followed 21 of the initial 50 patients and enrolled an additional 12 patients (n = 33 total). The mean age of patients was 4 years at the start of treatment (range, 3 wk–36 y). Therapeutic response was determined by improvements in liver function and weight. Results showed that 64% of patients responded to treatment, and two-thirds of patients survived longer than 3 years.

Approval of cholic acid for the treatment of peroxisomal disorders, including Zellweger spectrum disorders, was assessed in a single-arm study of 29 patients. Patients were followed over an 18-year period. An extension trial enrolled 10 of the 29 patients and recruited an additional 2 patients.
The majority of patients were younger than 2 years at the start of treatment (range, 3 wk–10 y). Therapeutic response was determined in the same manner as the previous studies. Results showed that 46% of patients responded to treatment, and 42% of patients survived longer than 3 years.

Cholic acid has no known contraindications. Warnings and precautions include an exacerbation of liver impairment. If liver function worsens during use, cholic acid should be discontinued. The most common adverse reactions occurring in 1% or greater of patients include diarrhea, reflux esophagitis, malaise, jaundice, skin lesion, nausea, abdominal pain, intestinal polypl, urinary tract infection, and peripheral neuropathy. Cholic acid should be carefully monitored by an experienced hepatologist or pediatric gastroenterologist.

Concomitant use of cholic acid with bile salt efflux pump inhibitors (e.g., cyclosporine) should be avoided. If concomitant use is necessary, serum transaminases and bilirubin should be monitored closely. Cholic acid should be taken at least 1 hour before or 4 to 6 hours or more after a bile acid–binding resin or aluminum-based antacid. Table 4 provides more detail on use of cholic acid in pregnancy and lactation.

Before the approval of cholic acid, patients with BASDs had no approved treatment options. FDA is requiring a post-marketing observational study to assess the long-term safety of cholic acid.

Eluxadoline
Eluxadoline (Viberzi—Forest Pharmaceuticals) is a mu-opi-
oid receptor agonist indicated for irritable bowel syndrome with diarrhea (IBS-D) in adult men and women. In addition to activity as a mu agonist, eluxadoline also works as a delta opioid receptor antagonist and as a kappa opioid receptor agonist. These actions have effects locally in the gut to reduce abdominal pain and diarrhea in patients with IBS-D.23

Studies estimate that IBS affects 10% to 15% of adults in the United States.24 Only 5% to 7% of those affected have received a diagnosis of IBS. IBS is the most common disease diagnosed by gastroenterologists.25 Women are affected twice as often as men, and IBS is most commonly seen in people 45 years of age or younger.24

There are four types of IBS: IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), mixed IBS (IBS-M), and unsubtyped IBS (IBS-U). Patients with IBS experience symptoms that include pain or discomfort in the abdomen and changes in bowel movement patterns. IBS-D is characterized by loose or watery stools at least 25% of the time.25,26

The recommended starting dose of eluxadoline in adults with IBS-D is 100 mg twice daily, taken orally with food. For patients with no gallbladder, the recommended dose is 75 mg twice daily. No dose adjustments are necessary in older adult patients or in those with renal impairment. In mild to moderate hepatic impairment (Child-Pugh Class A or B), a reduced dose of 75 mg twice daily is recommended. For additional detailed dosing, see Table 2.

Use is contraindicated in patients with severe hepatic impairment. The eluxadoline dose should also be adjusted on the basis of toxicity. Should severe constipation develop lasting longer than 4 days, eluxadoline should be discontinued. In addition, patients with symptoms of Sphincter of Oddi spasm should discontinue use. Metabolism of eluxadoline has not been clearly established. Excretion is primarily through the feces (82.2%).23

In May 2012, FDA issued guidance to industry on how to conduct IBS studies.26 A treatment period of at least 8 weeks’ duration is recommended, followed by a randomized withdrawal design to address the need for maintenance treatment. In addition, the guidance recommends a primary endpoint that measures the effect on abnormal defecation and abdominal pain, and the analysis should compare response rates between the study drug and placebo. For studies conducted in IBS-D patients, the defecation component should be evaluated by assessing stool consistency using the Bristol Stool Form Scale.27 For more details about the Bristol Stool Form Scale, visit http://bowelcontrol.nih.gov/Bristol_Stool_Form_Scale_508.pdf. The guidance also outlines the definition of a “weekly responder” and a “daily responder” in both pain intensity and stool consistency.28

Two large randomized, double-blind, placebo-controlled trials were submitted to FDA for approval of eluxadoline.31 Patients with IBS-D (n = 2,428) were randomized to eluxadoline 75 mg, 100 mg, or placebo twice daily. The primary outcome was a composite endpoint that incorporated abdominal pain and stool consistency, based on the Bristol Stool Scale Score (BSSS). In both studies, analysis of efficacy occurred at weeks 12 and 26, although one study followed patients to 52 weeks to collect long-term safety data. Results for the composite endpoint for both strengths measured at 12 weeks were statistically significant in favor of eluxadoline; however, not all results were significant at 26 weeks.

In addition, analysis of individual endpoints (abdominal pain and BSSS response) revealed no difference between eluxadoline and placebo for improvement of abdominal pain. Based on these results, eluxadoline appears to provide most of its benefit in improving stool consistency. More patients in the eluxadoline group (1.0%–1.3%) experienced serious gastrointestinal adverse events compared with the placebo group (0.4%).31

Eluxadoline has many contraindications, including the following:23

- Known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction
- History of pancreatitis or structural diseases of the pancreas, including known or suspected pancreatic duct obstruction
- Alcoholism, alcohol abuse, or alcohol addiction, or in patients who drink more than three alcoholic beverages per day
- Severe hepatic impairment (Child-Pugh Class C)
- History of chronic or severe constipation or sequelae from constipation, or known or suspected mechanical gastrointestinal obstruction

Warnings and precautions for eluxadoline are related to the drug’s adverse effects. Eluxadoline may cause pancreatitis unrelated to sphincter of Oddi dysfunction. Most cases were associated with excessive alcohol intake and resolved with discontinuation of the drug.

Use of eluxadoline may also lead to sphincter of Oddi spasm resulting in pancreatitis or elevated hepatic transaminases. Patients without a gallbladder are at an increased risk for sphincter of Oddi spasm, which most often occurred during the first week of therapy and resolved with discontinuation of the drug.

Concentrations of eluxadoline are increased in patients with hepatic impairment; hence the contraindication in severe hepatic impairment. Metabolism of eluxadoline is unclear. Product labeling recommends monitoring patients taking strong inhibitors of CYP isoenzymes because of the potential for increased exposure to eluxadoline. When eluxadoline is coadministered with OATP1B1 inhibitors (e.g., cyclosporine and gemfibrozil), the dose should be reduced to 75 mg twice daily.23 See Table 7 for additional eluxadoline drug interaction concerns.

Adverse reactions occurring in 5% or greater of patients include constipation, nausea, and abdominal pain. Table 4 includes pregnancy and lactation information for eluxadoline. Efficacy and safety in pediatric patients have not been established.23

Approval of eluxadoline provides another option for patients with IBS-D, although its place in therapy remains unclear. Of note, eluxadoline may have some potential for abuse
and dependence. In overdose, an opioid antagonist (i.e. naloxone) should be considered.

Eluxadoline is expected to be a controlled medication, and scheduling of the agent by the Drug Enforcement Administration is pending.

**New endocrinology agent: Parathyroid hormone**

Parathyroid hormone (Natpara—NPS) is FDA approved to control hypocalcemia in patients with hypoparathyroidism who are already taking calcium and vitamin D supplementation. Because of the risk of osteosarcoma, synthetic parathyroid hormone is indicated only for patients who are not well controlled on calcium supplements and active forms of vitamin D alone. Parathyroid hormone has not been studied in patients with acute postsurgical hypoparathyroidism or in patients with hypoparathyroidism caused by calcium receptor mutations.23

Hyypoparathyroidism is a rare disease that affects approximately 60,000 people in the United States. Several causes of hypoparathyroidism include destruction of the parathyroid glands, either by autoimmune causes or secondary to surgical removal; altered regulation of parathyroid hormone (PTH) production; impaired PTH action; or abnormal gland development. PTH helps regulate calcium and phosphorus levels in the body as well as vitamin D indirectly in the gut. Low levels of PTH lead to hypocalcemia. Patients with hypoparathyroidism manifest signs and symptoms of hypocalcemia. These may include neuromuscular irritability (tetany), peri-oral numbness, paresthesias of the hands and feet, muscle cramps, and potentially, arrhythmias and seizures.24 Long-term complications of hypoparathyroidism may include kidney damage, kidney stones, cataracts, and calcification of soft tissues.

Parathyroid hormone raises serum calcium via multiple mechanisms. It increases reabsorption of calcium from renal tubules and it increases intestinal calcium absorption by converting vitamin D to its active form and by increasing bone turnover (i.e., osteoclastic activity), thereby releasing calcium into the bloodstream.25

One 100-mcg subcutaneous dose of parathyroid hormone provides a 24-hour calcemic response in patients with hypoparathyroidism. Recombinant parathyroid hormone is available in four strengths as a once-daily subcutaneous injection (Table 2).22

Efficacy of parathyroid hormone was evaluated in 124 patients in a 24-week, randomized, double-blind, placebo-controlled trial (REPLACE). Patients with established hypoparathyroidism were randomized (2:1) to parathyroid hormone or placebo. All patients were receiving calcium and active forms of vitamin D supplementation. The average age of patients was 47 years, and most were female (79%) and Caucasian (96%). Patients had hypoparathyroidism for 15 years on average, and the cause was due to postsurgical complications in 71% of cases.24

Prior to randomization, all participants had calcium and active vitamin D doses adjusted to achieve an albumin-corrected serum calcium concentration between 8.0 and 9.0 mg/dL, and vitamin D was replaced in patients with low levels. Baseline serum calcium was 8.6 mg/dL, and participants received an average calcium dose of 2,000 mg per day. The median dose of oral active vitamin D was equivalent to 0.75 mcg daily of calcitriol.

Patients were randomized to recombinant parathyroid hormone 50 mcg daily or placebo for 24 weeks. Active forms of vitamin D were reduced by 50% at the time of randomization. The primary endpoint was the proportion of patients at week 24 who achieved a 50% or greater reduction from baseline in their daily dose of oral calcium and active vitamin D while maintaining a serum calcium level at or above their baseline value and at or below the upper limit of normal.

Forty-eight (53%) patients in the parathyroid hormone group achieved the primary endpoint, versus one (2%) patient in the placebo group. The proportion of patients who experienced at least one adverse effect and the proportion of patients with a serious adverse effect were similar between groups. In addition, results showed 42% of participants treated with parathyroid hormone achieved normal serum calcium levels on reduced doses of calcium and active forms of vitamin D supplements, compared with 3% of placebo-treated participants.24

Parathyroid hormone has no listed contraindications. Warnings and precautions are numerous. A boxed warning exists for osteosarcoma because of observations in studies with rodents. Whether parathyroid hormone causes osteosarcoma in humans is unknown. It is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS). Occurrence of osteosarcoma was dependent on dose and treatment duration.22

Severe hypercalcemia and hypocalcemia have been reported. The risk of hypercalcemia is highest when starting or increasing the dose. The risk of hypocalcemia is highest when the dose is withheld, missed, or abruptly discontinued but may occur at any time. Serum calcium levels as well as signs and symptoms of hypocalcemia should be monitored closely. Parathyroid hormone interacts indirectly with digoxin. Hypercalcemia of any cause may predispose patients to digoxin toxicity. Although no drug interaction study has been conducted with digoxin, patients should have their serum calcium monitored more frequently when taking digoxin concomitantly.25

The most common adverse effects of parathyroid hormone, occurring in 10% or more of individuals, are paresthesia, hypocalcemia, headache, hypercalcemia, nausea, hypoaesthesia, diarrhea, vomiting, arthralgia, hypercalcuiar, and pain in extremity.22

In terms of specific patient populations, pregnancy and lactation information for parathyroid hormone can be found in Table 4. Safety and efficacy in pediatric patients have not been established. No dosage adjustment is necessary in older adult patients or in patients with renal or hepatic impairment.22
This product offers an alternative to patients whose hypocalcemia cannot be controlled on calcium supplementation and active forms of vitamin D. Additional information about treatment of chronic hypoparathyroidism in adults can be found in the recently published guideline from the European Society of Endocrinology.

**New pulmonology agent: Lumacaftor/ivacaftor**

Lumacaftor/ivacaftor (Orkambi—Vertex) is a fixed-dose combination of lumacaftor, a cystic fibrosis transmembrane conductance regulator (CFTR) corrector, and ivacaftor, a CFTR potentiator. Lumacaftor/ivacaftor is indicated for the treatment of people with cystic fibrosis (CF) aged 12 years and older who have two copies of the F508del mutation in the CFTR gene. It is indicated for use only in patients who can be genetically identified as having the F508del mutation; efficacy and safety in patients with CF without the mutation have not been established. The CF combination drug was given breakthrough therapy designation, expedited review, and orphan drug designation.

CF is the most common fatal autosomal recessive disease among Caucasians, affecting about 30,000 people in the United States. According to the Cystic Fibrosis Foundation, life expectancy of a person with CF in the United States is 41 years. In CF, a person inherits two defective CFTR genes, one from each parent, which leads to the development of CF.

Patients with the F508del mutation produce an abnormal protein that disrupts how water and chloride are transported in the body. Eventually, this imbalance leads to a buildup of thick mucus in the lungs, pancreas, and other organs, which in turn can lead to the inability to properly digest and absorb food and respiratory failure. Patients most commonly present with pulmonary infections, pancreatic insufficiency, and elevated sweat chloride levels.

Ivacaftor (Kalydeco—Vertex) was first FDA approved in 2012 and is currently indicated to treat patients with CF aged 6 years and older with G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R mutations in the CFTR gene. Ivacaftor is a CFTR potentiator, which helps keep the CFTR protein channels on the cell surface open longer to increase the intra- and extracellular flow of salt and water. Lumacaftor is a CFTR corrector, which helps CFTR proteins reach the cell surface.

Lumacaftor and ivacaftor are both approximately 99% protein bound. Lumacaftor is primarily bound to albumin and ivacaftor to alpha 1-acid glycoprotein and albumin. Lumacaftor is not extensively metabolized, whereas ivacaftor is extensively metabolized. The combination drug is available as a fixed-dose tablet containing 200 mg of lumacaftor and 125 mg of lumacaftor/ivacaftor. The recommended dose is two tablets orally every 12 hours.

Approval of lumacaftor/ivacaftor was based on two double-blind, placebo-controlled trials (TRAFFIC and TRANS-PORT trials) of 1,108 patients with cystic fibrosis. Participants were 12 years or older and had the F508del mutation. In both studies, patients were randomized to two lumacaftor/ivacaftor tablets every 12 hours or placebo for 24 weeks. The primary endpoint was change in forced expiratory volume in 1 second (FEV1) from baseline at week 24. The average FEV1 at baseline was 61% of the predicted value. Overall, lumacaftor/ivacaftor improved FEV1, and pooled analyses showed the rate of pulmonary exacerbations was 30% to 39% lower in the lumacaftor/ivacaftor group. The discontinuation rate due to adverse events was 4.2% among patients treated with lumacaftor/ivacaftor compared with 1.6% among those who received placebo.

There are no contraindications for use of lumacaftor/ivacaftor; however, numerous warnings and precautions are as follows:

- Advanced liver disease: use with caution in these patients and only if the benefits are expected to outweigh the risks. Monitor closely after treatment initiation. A dosage adjustment is recommended in patients with moderate to severe impairment (Child-Pugh Class B or C).
- Liver-related events: elevated transaminases—alanine transaminase (ALT) and aspartate aminotransferase (AST)—have been observed in some cases associated with elevated bilirubin. Patients should have baseline ALT, AST, and bilirubin levels drawn and then have the levels tested every 3 months during the first year of therapy. After the first year, testing should be done annually.
- Respiratory events: chest discomfort, dyspnea, and abnormal respiration were observed more commonly during initiation. Clinical experience in patients with percent predicted FEV1 (ppFEV1) of less than 40 is limited. These patients may require additional monitoring during initiation of the drug.
- Drug interactions: coadministration with CYP3A substrates with a narrow therapeutic index or with strong CYP3A inducers is not recommended.
- Cataracts: noncongenital lens opacities/cataracts have been reported in pediatric patients. Baseline and follow-up examinations are recommended in pediatric patients initiating treatment with lumacaftor/ivacaftor.

The most common adverse effects of lumacaftor/ivacaftor, occurring in 5% or greater of patients, include dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, abnormal respirations, elevated blood creatine phosphokinase, rash, flatulence, rhinorrhea, and influenza. Women who took lumacaftor/ivacaftor also had increased menstrual abnormalities such as increased bleeding.

Lumacaftor/ivacaftor is listed as Pregnancy Category B. No studies in humans have investigated the effects on breastfed infants, and caution should be used when administered to women who are breastfeeding. Safety and efficacy of lumacaftor/ivacaftor in patients younger than age 12 have not been established. No dose adjustment is necessary for patients with mild hepatic impairment, although a dose reduction is recommended for patients with moderate hepatic impairment. No dose adjustment is necessary for patients with
mild to moderate renal impairment, but caution is advised in patients with severe or end-stage renal disease.36

This is the first CF drug directed at treating the cause of the disease in people who have two copies of a specific mutation. Of note, an expanded approval of lumacaftor/ivacaftor for children aged 6 to 11 years is expected in 2016.

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

References
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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. CPE 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 November 1, 2018, can receive CPE credit. Your statement of credit will be available upon successful completion of the assessment and evaluation and will be available on CPE Monitor for future viewing/printing.

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CPE assessment

Instructions: This assessment must be taken online; please see the “CPE information” sidebar on the previous page 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 medication binds to the P2Y12 receptor?
   a. Ivabradine
   b. Lumacaftor/ivacaftor
   c. Deoxycholic acid
   d. Cangrelor

2. How does Zarxio differ from Neupogen?
   a. Zarxio was superior to Neupogen in duration of severe neutropenia.
   b. Zarxio has one fewer indication than Neupogen.
   c. Zarxio has more severe adverse events than Neupogen.
   d. Zarxio has different strengths than Neupogen.

3. Which of the following drug : indication pairings is correct?
   a. Ivabradine : chronic heart failure
   b. Deoxycholic acid : bile acid synthesis disorders
   c. Eluxadoline : cystic fibrosis
   d. Cholic acid : reduction of submental fat

4. Which of the following drugs is administered subcutaneously?
   a. Cangrelor
   b. Cholic acid
   c. Parathyroid hormone
   d. Ivabradine

5. Which of the following statements is correct?
   a. Cholic acid is approved to treat bile acid synthesis disorders.
   b. Filgrastim-sndz is dosed 480 mcg once daily for all indications.
   c. Patients taking cholic acid should have their renal function monitored every 3 months.
   d. Biosimilar agents will be listed in the Orange Book.

6. With the use of which of the following agents is bleeding the most important risk?
   a. Lumacaftor/ivacaftor
   b. Ivabradine
   c. Eluxadoline
   d. Cangrelor

7. Which of the following statements is correct about ivabradine?
   a. Ivabradine should be taken on an empty stomach.
   b. Ivabradine is safe in pregnancy.
   c. Ivabradine is contraindicated if a patient’s blood pressure is less than 90/50 mm Hg.
   d. Ivabradine should not be used in conjunction with beta blockers.

8. Which of the following statements is correct about ivabradine?
   a. The starting dose of ivabradine for most patients is 2.5 mg twice daily.
   b. Ivabradine may cause luminous phenomena.
   c. Ivabradine is an If(f) channel stimulator.
   d. Ivabradine is contraindicated in renal impairment.

9. Which of the following statements is correct about cangrelor?
   a. Cangrelor reduced the occurrence of myocardial infarction during percutaneous coronary intervention procedures.
   b. Cangrelor reduced the risk of death.
   c. Cangrelor did not reduce the need for further revascularization.
   d. Cangrelor bleeding rates were less common than rates for clopidogrel.

10. Which of the following statements is correct about cangrelor?
    a. Glycoprotein IIb/IIIa inhibitors should be administered concomitantly with cangrelor during percutaneous coronary intervention.
    b. Cangrelor requires a dosage adjustment in hepatic impairment.
    c. Once the cangrelor infusion is discontinued, an oral antiplatelet should be administered immediately.
    d. Cangrelor should be initiated at a dose of 4 mcg/kg/min.

11. Which of the following statements is correct about eluxadoline?
    a. Eluxadoline is contraindicated in patients with a history of pancreatitis.
    b. Eluxadoline is contraindicated in active bleeding.
    c. Eluxadoline is contraindicated in renal impairment.
    d. Eluxadoline is contraindicated in the presence of infection.

12. Which of the following statements is correct about eluxadoline?
    a. Eluxadoline is a mu, kappa, and delta receptor agonist.
    b. Eluxadoline is approved for use in irritable bowel syndrome with constipation.
    c. Eluxadoline is dosed 75 mg twice daily in patients with no gallbladder.
    d. Eluxadoline has no potential for abuse.
13. Which of the following statements is correct about parathyroid hormone?
   a. Parathyroid hormone is approved for use as first-line treatment in hypoparathyroidism.
   b. Parathyroid hormone raises calcium by direct action at calcium receptors.
   c. Parathyroid hormone has no known drug interactions.
   d. Parathyroid hormone labeling includes a black box warning for osteosarcoma.

14. Which of the following statements is correct about parathyroid hormone?
   a. Parathyroid hormone should be dose adjusted in renal impairment.
   b. The most common adverse effects of parathyroid hormone include dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, and fatigue.
   c. The maximum dose of parathyroid hormone is 100 mcg SubQ daily.
   d. Cholecalciferol is an acceptable form of vitamin D for patients with hypoparathyroidism.

15. Which of the following statements is correct about lumacaftor/ivacaftor?
   a. Women who took lumacaftor/ivacaftor had increased menstrual abnormalities, such as increased bleeding.
   b. Lumacaftor is a CFTR potentiator, which helps keep the CFTR protein channels on the cell surface open longer to increase the intra- and extracellular flow of salt and water.
   c. Ivacaftor is a CFTR corrector, which helps CFTR proteins reach the cell surface.
   d. Lumacaftor/ivacaftor is contraindicated in patients with advanced liver disease.

16. Which of the following statements is correct about lumacaftor/ivacaftor?
   a. Lumacaftor/ivacaftor is approved for all patients with cystic fibrosis.
   b. Lumacaftor/ivacaftor is a Pregnancy Category C drug.
   c. Pediatric patients taking lumacaftor/ivacaftor should have a baseline ophthalmologic examination.
   d. Lumacaftor/ivacaftor improved FEV₁, but did not reduce pulmonary exacerbations.

17. Which of the following statements is correct about cholic acid?
   a. Use of cholic acid is contraindicated in Zellweger spectrum disorders.
   b. Cholic acid is dosed 5 mcg to 10 mcg/kg/d in divided doses.
   c. The most common adverse effects of cholic acid include injection site edema and swelling, hematoma, pain, numbness, and erythema.
   d. Concomitant use of cholic acid with bile salt efflux pump inhibitors should be avoided.

18. Which of the following statements is correct about deoxycholic acid?
   a. It is approved to treat the appearance of abdominal fat.
   b. It is contraindicated in the presence of rosacea.
   c. Marginal mandibular nerve injury may occur with incorrect injection technique.
   d. Up to 50 injections may be administered every 2 weeks.

19. Which of the following statements is correct about filgrastim-sndz?
   a. Tbo-filgrastim and filgrastim-sndz are both biosimilar to Neupogen.
   b. Filgrastim-sndz completed placebo-controlled trials to demonstrate biosimilarity.
   c. To be deemed “highly similar,” filgrastim-sndz may differ in pharmacodynamics.
   d. Filgrastim-sndz was approved via the 351(k) biosimilar pathway.

20. Which of the following is administered intravenously?
   a. Cangrelor
   b. Filgrastim-sndz
   c. Parathyroid hormone
   d. Deoxycholic acid