Abstract

Objective: To provide information about the most important properties of new therapeutic agents approved by FDA and first marketed in 2015.

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

Data synthesis: This review covers 11 new therapeutic agents approved in the United States in 2015: sacubitril/valsartan, alirocumab, evolocumab, sonidegib, rolapitant, trifluridine/tipiracil, daratumumab, ixazomib, elotuzumab, daclatasvir, and uridine triacetate. Indications and information on dosage and administration for these agents are reviewed, as are the most important pharmacokinetic properties, drug interactions, efficacy and safety, and other precautions. Practical considerations for the use of these new agents also are discussed. Whenever possible, the properties of the new drugs are compared with those of the older agents marketed for the same indications.

Summary: Sacubitril/valsartan combines an angiotensin receptor blocker (ARB) with sacubitril, a novel first-in-class neprilysin inhibitor for the treatment of chronic heart failure. Alirocumab and evolocumab are two new proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors approved for the treatment of hyperlipidemia in combination with statins. Sonidegib is a Hedgehog pathway inhibitor approved for basal cell carcinoma. Rolapitant is a substance P/neurokinin-1 (NK-1) receptor antagonist for the treatment of chemotherapy-induced nausea and vomiting. Trifluridine/tipiracil is a combination agent approved for the treatment of advanced metastatic colorectal cancer for patients who have failed previous therapies. Three new agents have been approved for the treatment of multiple myeloma: daratumumab is for patients who have tried at least three other regimens; ixazomib is for patients who have tried at least one other regimen; and elotuzumab is for those who have received one to three prior therapies. Daclatasvir is a new antiviral for patients with hepatitis C virus (HCV) genotype 3. Uridine triacetate provides a treatment option for patients with rare hereditary orotic aciduria.
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. Sacubitril/valsartan
   b. Rolapitant
   c. Alirocumab
   d. Daratumumab

2. Which of the following statements is correct?
   a. Uridine triacetate has been granted orphan drug status for hereditary orotic aciduria.
   b. Daratumumab is a reversible proteasome inhibitor.
   c. Rolapitant may cause fetal toxicity.
   d. Trifluridine/tipiracil is indicated for locally advanced basal cell carcinoma.

3. Which of the following statements is correct about sonidegib?
   a. It is indicated for locally advanced basal cell carcinoma.
   b. It is administered intravenously.
   c. It should be taken with food.
   d. It may cause significant hypersensitivity reactions.

Objectives
The third part of this four-part series on new therapeutics approved in the United States in 2015 covers 11 new drugs: sacubitril/valsartan, alirocumab, evolocumab, sonidegib, rolapitant, trifluridine/tipiracil, daratumumab, ixazomib, elotuzumab, daclatasvir, and uridine triacetate (Table 1).

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.1 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.1

Sacubitril/valsartan
Sacubitril/valsartan (Entresto—Novartis) is a new combination of generic valsartan and the new molecular entity sacubitril. The combination is indicated to reduce the risk of cardiovascular death or hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction.2

Sacubitril is a prodrug with a novel mechanism of action. It inhibits neprilysin (neutral endopeptidase [NEP]) through the active metabolite LBQ657. This leads to an increased level of peptides, including natriuretic peptides, thus decreasing vasoconstriction, sodium retention, and maladaptive remodeling. Valsartan is an angiotensin II receptor blocker (ARB).2

Pertinent kinetics of the combination are that sacubitril is converted to an active metabolite with a long half-life of 11.5 hours and primarily eliminated in urine, and valsartan is primarily eliminated in feces (Table 2).2

Sacubitril/valsartan is a fixed-dose combination given orally twice daily. After 2 to 4 weeks, the dose should be doubled. The lowest available dose (24 mg/26 mg) is used in severe renal insufficiency (<30 mL/min) or moderate hepatic impairment (Child-Pugh Class B); its use in severe hepatic impairment is not recommended. See Table 3 for additional details on dosing.2 Of note, the valsartan salt in this combination product is different from that in the generically available version.

Efficacy of sacubitril/valsartan was evaluated in two randomized, double-blind, placebo-controlled trials. The 36-week Phase II PARAMOUNT study compared the combination sacubitril/valsartan to valsartan alone.1 PARADIGM-HF, a larger (n = 8,442) Phase III study of 27 months’ duration, compared sacubitril/valsartan to enalapril alone.4 The primary endpoint of PARADIGM-HF was a composite of death from cardiovascular causes or first hospitalization for heart failure. Included patients were aged 18 years or older, had New York Heart Association (NYHA) Class II–IV heart failure and an ejection fraction (EF) of 40% or less, were taking stable doses of beta blockers and angiotensin-converting enzyme (ACE) inhibitors/ARBs, and had elevated brain natriuretic peptide (BNP) levels.4

The study was stopped early because a prespecified interim analysis showed that angiotensin receptor–neprilysin inhibition with combination sacubitril/valsartan was superior to ACE inhibition alone in reducing the risk of death or hospitalization for heart failure. Safety and tolerability including any adverse event, serious adverse events, and events leading to discontinuation was similar between groups.4

It is important to note that results of the study cannot be extrapolated to patients with heart failure with a preserved ejection fraction (HFrEF). Other limitations exist, including any adverse event, serious adverse events, and events leading to discontinuation was similar between groups.4

In the PARAMOUNT phase IIb study, the primary endpoint was a composite of all-cause death or hospitalization for heart failure. The 24-week phase IIb study enrolled patients (~70%) had NYHA Class II heart failure.4 Patients were on a high dose of valsartan, while the majority of patients (~70%) had NYHA Class II heart failure.4

Sacubitril/valsartan may cause fetal toxicity, and the drug should be discontinued as soon as possible when pregnancy is detected. Table 4 includes details about pregnancy and lactation. Additional contraindications include concomitant use of aliskiren in patients with diabetes and concomitant use or use within 36 hours of an ACE inhibitor because of the risk of serious angioedema. Warnings and precautions for the combination are similar to those for other ARBs.2

The most common adverse effects of sacubitril/valsartan include hypotension (18%), hyperkalemia (4%–16%), and increased serum creatinine (1%–16%). Additional adverse reactions include orthostasis, dizziness, angioedema, and decreased hemoglobin and hematocrit levels. This combination drug should not be used in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy.2

Numerous drug interactions exist. Most are related to an enhanced hypotensive effect, such as with potassium sparing diuretics, where therapy should be monitored. Use with other ACE inhibitors should be avoided because of the in-
creased risk of angioedema. Therapy modifications should be considered when used with aliskiren, amifostine, obinutuzumab, sodium phosphates, and lithium.2

Monitoring of sacubitril/valsartan includes baseline and periodic serum potassium, renal function, and blood pressure.2

While sacubitril/valsartan provides another treatment option for patients with heart failure, ACEs, ARBs, and beta-blockers remain the standards of care. The combination drug’s place in therapy has yet to be determined.

**Alirocumab and evolocumab**

Familial hypercholesterolemia (FH) is an autosomal-dominant genetic disease present in all racial and ethnic groups that leads to premature atherosclerotic cardiovascular disease (ASCVD). The genetic basis of the disorder is an impaired functioning of the low-density lipoprotein (LDL) receptor.1–5 Heterozygous FH (HeFH) has the highest prevalence of genetic defects that cause significant premature mortality (1:200 to 1:500 or higher in affected populations).

In 2015, two new human monoclonal antibodies were approved to help reduce LDL cholesterol. Alirocumab (Praluent—Sanofi Regeneron) and evolocumab (Repatha—Amgen) both reduce LDL by inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9). (See Table 3.) PCSK9 is an enzyme found in the liver that is involved in cholesterol homeostasis. LDL is removed from blood when it binds to LDL receptors (LDLRs) on the surface of liver cells. PCSK9 degrades LDLRs, which decreases metabolism of LDL, leading to an increase in plasma concentrations. PCSK9 inhibitors increase LDLRs, resulting in a decrease in plasma LDL by 65% to 70% even as add-on therapy to maximally tolerated doses of statins.

Alirocumab is indicated for HeFH or ASCVD. Evolocumab is also indicated for HeFH but has an additional indication for homozygous familial hypercholesterolemia (HoFH) and can be used in adolescents with HoFH. Both are intended as

<table>
<thead>
<tr>
<th>Table 1. New therapeutic drugs approved in 2015: Part 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic name</strong></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td><strong>Cardiology</strong></td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
</tr>
<tr>
<td><strong>Alirocumab</strong></td>
</tr>
<tr>
<td><strong>Evolocumab</strong></td>
</tr>
<tr>
<td><strong>Hematology/oncology</strong></td>
</tr>
<tr>
<td><strong>Sonidegib</strong></td>
</tr>
<tr>
<td><strong>Rolapitant</strong></td>
</tr>
<tr>
<td><strong>Trifluridine/ tipiracil</strong></td>
</tr>
<tr>
<td><strong>Daratumumab</strong></td>
</tr>
<tr>
<td><strong>Ixazomib</strong></td>
</tr>
<tr>
<td><strong>Elotuzumab</strong></td>
</tr>
<tr>
<td><strong>Infectious disease</strong></td>
</tr>
<tr>
<td><strong>Daclatasvir</strong></td>
</tr>
<tr>
<td><strong>Genetic disease</strong></td>
</tr>
<tr>
<td><strong>Uridine triacetate</strong></td>
</tr>
</tbody>
</table>

Abbreviations used: SubQ, subcutaneous; HCV, hepatitis C virus; 5-FU, 5-fluorouracil.

Sources: Refs. 2, 3, 12, 15, 18, 21, 24, 26, 28, 30, 33.
Because homozygous FH is rare, this article will focus on non-HoFH studies. In the non-HoFH population, also known as primary hyperlipidemia, four randomized, double-blind, placebo- or ezetimibe-controlled studies are reviewed (Table 6). Three of the studies were 12 weeks, and one was a 52-week, placebo-controlled trial. Of note, each treatment arm had different inclusion criteria and the studies only observed the surrogate markers and not clinical outcomes. The primary outcome of these studies was change in LDL from baseline.

Table 6 provides an overview of four evolocumab studies with results. Overall, treatment with evolocumab reduced LDL 52% to 64% from baseline in patients with ASCVD or HeFH compared with placebo, which ranged from an increase in LDL of 9% to a decrease of 1% (Table 6).

In summary, evolocumab reduced LDL by 50%, and placebo increased LDL by 7%.

Evolocumab is dosed 75 mg subcutaneously once every 2 weeks. The dose may be increased to 150 mg once every 2 weeks if an adequate response is not achieved within 4 to 8 weeks.

Evolocumab is given subcutaneously 140 mg or 420 mg once monthly in HoFH or 140 mg every 2 weeks or 420 mg once monthly in HeFH or ASCVD. If switching between the two agents is required, administer the first dose of the new regimen on the next scheduled day of the prior regimen. No

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacubitril/valsartan</td>
<td>Entresto</td>
<td>Sacubitril: prodrug that inhibits neprilysin (neutral endopeptidase) through the active metabolite LBQ657, leading to increased levels of peptides, including natriuretic peptides. Valsartan: angiotensin II receptor blocker.</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>Praluent</td>
<td>Human monoclonal antibody directed against PCSK9. Binds to PCSK9 and inhibits circulating PCSK9 from binding to the LDL receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. By inhibiting the binding of PCSK9 to LDLR, PCSK9 inhibitors increase the number of LDLRs available to clear LDL from the blood, thereby lowering LDL levels.</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>Repatha</td>
<td>Same as above.</td>
</tr>
<tr>
<td>Sonidegib</td>
<td>Odomzo</td>
<td>Basal cell cancer is associated with mutations in Hedgehog pathway components. Sonidegib is a selective Hedgehog pathway inhibitor that binds to and inhibits SMO, the transmembrane protein involved in Hedgehog signal transduction.</td>
</tr>
<tr>
<td>Rolapitant</td>
<td>Varubi</td>
<td>Selective and competitive antagonist of human substance P/neurokinin-1 receptors.</td>
</tr>
<tr>
<td>Trifluridine/ tipiracil</td>
<td>Lonsurf</td>
<td>Inhibits the growth of CD38-expressing tumor cells by inducing apoptosis directly through Fc-mediated cross linking as well as by immune-mediated tumor cell lysis through complement-dependent cytotoxicity; antibody-dependent, cell-mediated cytotoxicity; and antibody-dependent cellular phagocytosis.</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>Darzalex</td>
<td>Reversible proteasome inhibitor that preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome.</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>Ninlaro</td>
<td>Humanized IgG1 monoclonal antibody that specifically targets the SLAMF7 protein. Directly activates natural killer cells.</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>Empliciti</td>
<td>Binds to the N-terminus within Domain 1 of HCV NS5A and inhibits viral RNA replication and virion assembly.</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Daklinza</td>
<td>Prodrug of uridine that is converted to uridine triphosphate, which competes with fluorouridine triphosphate for incorporation into RNA, thereby preventing cell death and dose-limiting fluorouracil toxicity.</td>
</tr>
<tr>
<td>Uridine triacetate</td>
<td>Xuriden</td>
<td>Basal cell cancer is associated with mutations in Hedgehog pathway components. Sonidegib is a selective Hedgehog pathway inhibitor that binds to and inhibits SMO, the transmembrane protein involved in Hedgehog signal transduction.</td>
</tr>
</tbody>
</table>

**Table 2.** Mechanism of action of new therapeutic agents

Abbreviations used: PCSK9, proprotein convertase subtilisin/kexin type 9; SMO, smoothened; IgG1, immunoglobulin G1; SLAMF7, signaling lymphocytic activation molecule, family member 7; HCV, hepatitis C virus; NS5A, nonstructural protein 5A. Sources: Refs. 2, 9, 12, 15, 18, 21, 24, 26, 28, 30, 33.
### Table 3. 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>Sacubitril/valsartan</td>
<td>Entresto</td>
<td>Tablet, oral: sacubitril 24 mg/valsartan 26 mg; sacubitril 49 mg/valsartan 51 mg; sacubitril 97 mg/valsartan 103 mg</td>
<td>Start with sacubitril 49 mg and valsartan 51 mg twice daily. Double the dose as tolerated after 2–4 weeks to target maintenance dose of sacubitril 97 mg and valsartan 103 mg twice daily.</td>
<td>Patients previously taking low doses of an ACE inhibitor or ARB, or not currently taking an ACE inhibitor or ARB, should start with sacubitril 24 mg and valsartan 26 mg twice daily. Concomitant use of an ACE inhibitor is contraindicated; allow a 36-hour washout period when switching from or to an ACE inhibitor.</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>Praluent</td>
<td>Injectable, single-dose prefilled syringes: 75 mg, 150 mg</td>
<td>75 mg SubQ once every 2 weeks; 150 mg SubQ once every 2 weeks</td>
<td>Start with 75 mg; if LDL-C response is inadequate, increase to 150 mg.</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>Repatha</td>
<td>140-mg/mL prefilled syringe and SureClick autoinjector</td>
<td>Hyperlipidemia, primary: 140 mg SubQ every 2 weeks or 420 mg SubQ once monthly in abdomen, thigh, or upper arm; HoFH: 420 mg once monthly</td>
<td>To administer 420 mg, give three 140-mg injections consecutively within 30 minutes.</td>
</tr>
<tr>
<td>Sonidegib</td>
<td>Odomzo</td>
<td>Capsules, oral: 200 mg</td>
<td>Basal cell carcinoma, locally advanced: 200 mg once daily until disease progression or unacceptable toxicity</td>
<td>Should be taken on an empty stomach at least 1 hour before or 2 hours after a meal.</td>
</tr>
<tr>
<td>Rolapitant</td>
<td>Varubi</td>
<td>Tablet, oral: 90 mg</td>
<td>180 mg approx. 1–2 hours prior to moderately or highly emetogenic chemotherapy</td>
<td>Give in combination with dexamethasone and a 5-HT3 receptor antagonist. May be administered without regard to meals; should not be taken more than once every 2 weeks.</td>
</tr>
<tr>
<td>Trifluridine/tipiracil</td>
<td>Lonsurf</td>
<td>Tablet, oral: trifluridine 15 mg/tipiracil 6.14 mg; trifluridine 20 mg/tipiracil 8.19 mg</td>
<td>35 mg/m²/dose up to max of 80 mg/dose based on trifluridine twice daily on days 1–5 and days 8–12 of each 28-day cycle</td>
<td>Should be taken within 1 hour after morning and evening meals.</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>Darzalex</td>
<td>Injectable solution in a single-dose vial: 100 mg/5 mL, 400 mg/20 mL</td>
<td>16 mg/kg body weight I.V. weekly for weeks 1–8, every 2 weeks for weeks 9–24, and every 4 weeks from week 25 until disease progression</td>
<td>Premedicate with corticosteroids, antipyretics, and antihistamines. Administer postinfusion medications (oral corticosteroids).</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>Ninlaro</td>
<td>Capsule, oral: 2.3 mg, 3 mg, and 4 mg</td>
<td>4 mg taken on days 1, 8, and 15 of a 28-day cycle</td>
<td>Should be taken at least 1 hour before or at least 2 hours after a meal.</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>Empliciti</td>
<td>Injectable 300-mg or 400-mg lyophilized powder for reconstitution</td>
<td>10 mg/kg administered I.V. every week for the first two cycles and every 2 weeks thereafter until disease progression or unacceptable toxicity</td>
<td>I.V. infusion only; not for I.V. push or bolus. Premedicate with dexamethasone, diphenhydramine, ranitidine, and acetaminophen approx. 45–90 minutes prior to elotuzumab.</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>Daklinza</td>
<td>Tablet, oral: 30 mg, 60 mg</td>
<td>Chronic hepatitis C (genotype 3): 60 mg/d with concomitant sofosbuvir for 12 weeks</td>
<td>Discontinue if sofosbuvir is permanently discontinued.</td>
</tr>
<tr>
<td>Uridine triacetate</td>
<td>Xuriden</td>
<td>Oral granules: single-use packets containing 2-g uridine triacetate in cartons of 30 packets each</td>
<td>60 mg/kg/d; increase to 120 mg/kg/d (maximum: 8 g/d)</td>
<td>May be mixed with food (e.g., applesauce, pudding, or yogurt) and administered immediately, followed by drinking at least 4 ounces of water. Granules should not be chewed.</td>
</tr>
</tbody>
</table>

Abbreviations used: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; HoFH, homozygous familial hypercholesterolemia; SubQ, subcutaneous; LDL-C, low-density lipoprotein cholesterol.

Sources: Refs. 2, 9, 12, 15, 16, 21, 24, 26, 28, 30, 33.
Dosage adjustment is necessary in renal impairment or hepatic impairment with either PCSK9 inhibitor. If a dose is missed, the drug should be administered as soon as possible if there are more than 7 days until the next scheduled dose, or the missed dose should be omitted and the next dose administered according to the original schedule. Table 2 lists detailed dosing information.

PCS Kathy inhibitors are currently available only from specialty pharmacies. Both agents are available as a pen auto-injector and a prefilled syringe. Of note, evolocumab and alirocumab are genetically produced from mouse cells (hamster).

Patients should be counseled to allow alirocumab and evolocumab solutions to come to room temperature for approximately 30 to 40 minutes prior to administration. Solutions should not be shaken or warmed with heat or hot water. Alirocumab must be discarded if exposed to room-temperature conditions for more than 24 hours. Evolocumab can be stored at room temperature but must be used within 30 days. Both agents should be administered by subcutaneous injection into the thigh, abdomen (except for the 2-inch area around the navel), or upper arm, and patients should rotate the injection site. PCSK9 inhibitors should not be injected

Table 4. Use of new therapeutic agents during pregnancy and lactation

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Pregnancy category</th>
<th>Comments</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacubitril/valsartan</td>
<td>Fetal toxicity</td>
<td>Discontinue as soon as possible once pregnancy is detected.</td>
<td>Not recommended; unknown if excreted in human milk</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>–</td>
<td>No adequate or well-controlled studies in pregnant women; adverse events were not observed in animal studies.</td>
<td>No data</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>–</td>
<td>Not studied</td>
<td>Not studied</td>
</tr>
<tr>
<td>Sonidegib</td>
<td>Fetal toxicity</td>
<td>Embryotoxic, fetotoxic, and teratogenic in animals. Do not use in females or males without proper protection. Verify pregnancy status before initiating.</td>
<td>Unknown; not recommended because of potential for serious adverse effects</td>
</tr>
<tr>
<td>Rolapitant</td>
<td>–</td>
<td>No adequate or well-controlled studies in pregnant women; adverse events were not observed in animal studies.</td>
<td>No data; caution; unknown if excreted in human milk</td>
</tr>
<tr>
<td>Trifluridine/tipiracil</td>
<td>Fetal toxicity</td>
<td>No data</td>
<td>No data; present in rat milk</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>–</td>
<td>To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of treatment.</td>
<td>No data; caution; IgG known to be present in human milk</td>
</tr>
<tr>
<td>Ixazomib</td>
<td>Fetal toxicity</td>
<td>May cause fetal harm when administered to a pregnant woman (women should avoid becoming pregnant); animal studies showed fetotoxicity. Male and female patients of childbearing potential must use effective contraceptive measures during and for 90 days following treatment.</td>
<td>Caution; unknown if excreted in human milk; advise women to discontinue nursing</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>Fetal toxicity</td>
<td>No data; fetotoxicity due to requirement of use with lenalidomide</td>
<td>No data</td>
</tr>
<tr>
<td>Daclatasvir</td>
<td>–</td>
<td>Adverse events were observed in animal studies.</td>
<td>Caution; unknown if excreted in human milk</td>
</tr>
<tr>
<td>Uridine triacetate</td>
<td>–</td>
<td>No adequate or well-controlled studies in pregnant women; adverse events were not observed in animal studies.</td>
<td>Caution; unknown if excreted in human milk</td>
</tr>
</tbody>
</table>

Abbreviation used: IgG, immunoglobulin G.
Sources: Refs. 2, 9, 12, 15, 18, 21, 24, 26, 28, 30, 33.

Table 5. Efficacy of alirocumab in placebo-controlled studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment vs. placebo (n)</th>
<th>% HeFH and ASCVD</th>
<th>LDL baseline (mg/dL)</th>
<th>% LDL reduction</th>
<th>% requiring 150 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Week 12</td>
<td>Week 24</td>
</tr>
<tr>
<td>1</td>
<td>1,553 vs. 788</td>
<td>18/69</td>
<td>122</td>
<td>NR</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>209 vs. 107</td>
<td>NR/84</td>
<td>102</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>3 &amp; 4</td>
<td>490 vs. 245</td>
<td>100/45</td>
<td>141</td>
<td>43</td>
<td>47</td>
</tr>
<tr>
<td>5</td>
<td>72 vs. 35</td>
<td>100/50</td>
<td>198</td>
<td>NR</td>
<td>43</td>
</tr>
</tbody>
</table>

Abbreviations used: HeFH, heterozygous familial hypercholesterolemia; ASCVD, atherosclerotic cardiovascular disease; NR, not reported.
Sources: Refs. 8–10.
The onset of peak effect is 4 to 8 hours for alirocumab and within about 4 hours for evolocumab. In terms of metabolism, PCSK9 inhibitors are expected to undergo polymersynthesis and be degraded to small peptides and amino acids. Bioavailability when given subcutaneously is approximately 85% with alirocumab and 72% with evolocumab. The half-life of these drugs is 17 to 20 days with alirocumab and 11 to 17 days with evolocumab. Time to steady state is reduced when administered with a statin (12 d).

Table 6. Efficacy of evolocumab in four select studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment arms</th>
<th>Treatment vs. placebo (n)</th>
<th>Patients</th>
<th>LDL baseline (mg/dL)</th>
<th>Week 12 LDL reduction (%)</th>
<th>Week 52 LDL reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>140 mg Q2W</td>
<td>105 vs. 42 ASCVD</td>
<td>ASCVD</td>
<td>108</td>
<td>64</td>
<td>+7</td>
</tr>
<tr>
<td></td>
<td>420 mg QM</td>
<td>105 vs. 44 ASCVD</td>
<td>ASCVD</td>
<td>108</td>
<td>58</td>
<td>+5</td>
</tr>
<tr>
<td>2</td>
<td>420 mg QM</td>
<td>95 vs. 44 ASCVD</td>
<td>ASCVD</td>
<td>105</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>140 mg Q2W</td>
<td>110 vs. 54 HeFH</td>
<td>HeFH</td>
<td>156</td>
<td>62</td>
<td>1</td>
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<tr>
<td></td>
<td>420 mg QM</td>
<td>110 vs. 55 HeFH</td>
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<td>156</td>
<td>56</td>
<td>+4</td>
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<tr>
<td>4</td>
<td>420 mg QM</td>
<td>33 vs. 16 HoFH</td>
<td>HoFH</td>
<td>349</td>
<td>22</td>
<td>+9</td>
</tr>
</tbody>
</table>

Abbreviations used: Q2W, every 2 weeks; QM, once monthly; ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia. Sources: Refs. 11, 12.

into areas of damaged skin or coadministered with other injectable drugs at the same injection site. Administration of 420 mg of evolocumab requires that three separate 140-mg injections be given consecutively within a 30-minute period.

Significant adverse reactions with alirocumab include injection site reaction (7%), influenza (6%), diarrhea (5%), myalgia (4%), liver enzyme disorder (3%), muscle spasm (3%), cough (3%), increased serum transaminases (>3 times the upper limit of normal; 2%), confusion and memory impairment (both <1%), and hypersensitivity reactions (<1%).

Significant adverse effects with evolocumab include nasopharyngitis (6%–11%), upper respiratory tract infection (9%), influenza (8%–9%), injection site reaction (6%), gastroenteritis (3%–6%), urinary tract infection (5%), cough (1%–5%), myalgia (4%), dizziness (4%), sinusitis (4%), hypertension (3%), fatigue (2%), nausea (2%), skin rash (1%), bruise (1%), and antibody development (<1%).

Hypersensitivity reactions (e.g., rash, urticaria) have been reported with both agents, with some patients requiring discontinuation. Because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty.

One drug interaction should be noted for both agents. Use of either alirocumab or evolocumab should be avoided with belimumab. Monoclonal antibodies may enhance the adverse/toxic effect of belimumab.

The onset of peak effect is 4 to 8 hours for alirocumab and within 4 hours for evolocumab. In terms of metabolism, PCSK9 inhibitors are expected to undergo polymersynthesis and be degraded to small peptides and amino acids. Bioavailability when given subcutaneously is approximately 85% with alirocumab and 72% with evolocumab. The half-life of these drugs is 17 to 20 days with alirocumab and 11 to 17 days with evolocumab. Time to steady state is reduced when administered with a statin (12 d).

Table 4 provides information about pregnancy and lactation concerns with the PCSK9 inhibitors. Both manufacturers state that the decision to continue or discontinue breastfeeding during therapy should take into account the risk of exposure to the infant and the benefits of treatment to the mother.

Monitoring of PCSK9 inhibitors should include measuring LDL-C levels 4 to 8 weeks after initiation. Response to PCSK9 inhibitors depends on the degree of the patients’ LDLR function.

Note that the effect of alirocumab and evolocumab on cardiovascular morbidity and mortality has not been determined. In addition, concerns with PCSK9 inhibitors causing neurocognitive adverse events remain. FDA has requested that neurocognitive testing be incorporated into long-term Phase III trials. Several long-term studies that will evaluate safety (e.g., EBBINGHAUS, OSLER, and ODYSSEY-Long Term) are under way.

In summary, the PCSK9 inhibitors have demonstrated significant LDL-lowering efficacy of 40% to 60% in clinical trials and an overall favorable safety profile. While these LDL reductions are dramatic, recent published guidelines have shifted clinical practice away from a focus on LDL targets and more toward encouraging use of statins as the mainstay of anticholesterol therapy given their proven cardiovascular risk reduction in large long-term studies. One additional issue is the high cost of these specialty drugs. Payers are concerned about how to cover them when the average cost is approximately $1,000 per month, the pool of potential patients is enormous, and these agents may be used indefinitely.

New hematology/oncology agents

More drugs used to treat cancer were approved in 2015 than drugs for any other group of diseases. Of the 45 novel drugs approved, 14 (31%) were antineoplastics. Cancer is the second-leading cause of death in the United States. According to the American Cancer Society, the disease is estimated to claim 1,630 American lives every day.

Basal cell carcinoma (BCC) is the most common type of skin cancer, accounting for approximately 80% of all skin cancers. BCC typically develops on sun-exposed areas. While usually slow-growing, it may spread into surrounding tissue if left untreated. BCC is associated with mutations in Hedgehog pathway components.

Sonidegib

Sonidegib (Odomzo—Novartis) is a Hedgehog pathway inhibitor indicated for the treatment of adult patients with locally advanced BCC that has recurred following surgery or radiation therapy, or those who are not candidates for sur-
gery or radiation therapy.15

Sonidegib joins vismodegib as the second FDA-approved inhibitor of the Hedgehog pathway. Sonidegib binds to and inhibits Smoothened (SMO), a transmembrane protein involved in Hedgehog signal transduction.15,16

The recommended dose of sonidegib is 200 mg orally once daily on an empty stomach, at least 1 hour before or 2 hours after a meal. Less than 10% of each oral dose is absorbed. A high-fat meal (approximately 1,000 calories, with 50% of calories from fat) was shown to increase the exposure to sonidegib greater than sevenfold, hence the recommendation for taking the drug on an empty stomach. See Table 2 for additional detailed dosing. The elimination half-life of sonidegib is approximately 28 days.15

No overall differences in effectiveness were observed between patients on the basis of age or sex, and safety and effectiveness of sonidegib have not been established in pediatric patients. In addition, no dose adjustment is recommended for patients with mild hepatic impairment, and the drug’s use in moderate or severe impairment has not been studied. Furthermore, no dose adjustment is recommended for patients with renal impairment.15

Efficacy of sonidegib was evaluated in patients with locally advanced BCC (n = 194) or metastatic BCC (n = 36) in a single, multicenter, double-blind, multiple-cohort trial.17 Patients were randomized (2:1) to receive either sonidegib 800 mg or 200 mg orally once daily until disease progression or intolerable toxicity.17

The primary endpoint of the study was objective response rate (ORR). Duration of response was a secondary endpoint. The ORR for sonidegib was 58%, consisting of 3 complete responses (5%) and 35 partial responses (53%). Among the 38 patients with an objective response, 7 (18%) experienced subsequent disease progression. The remaining 31 patients (82%) had ongoing responses ranging from 1.9 to 18.2 months; median duration of response had not been reached. Patients on higher doses of sonidegib (i.e., 800 mg/d) showed no better response rates than those taking 200 mg daily.17

Sonidegib has no contraindications; however, several warnings and precautions should be noted. Sonidegib-treated patients should be advised not to donate blood or blood products during treatment or at least 20 months after the last dose. In addition, musculoskeletal adverse reactions may occur. Serum creatinine kinase and creatinine levels should be obtained prior to initiating therapy, periodically during treatment, and as clinically appropriate. Based on the severity of musculoskeletal adverse reactions, a temporary dose interruption or discontinuation may be required.15 Renal function should also be assessed before initiation of the drug.

The most common adverse reactions of sonidegib (occurring in ≤10% of patients) are muscle spasms, alopecia, dysgeusia, fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight and appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus.

Use of sonidegib with strong cytochrome P450 (CYP) 3A inhibitors and long-term (greater than 14 days) use of moderate CYP3A inhibitors should be avoided. In addition, strong and moderate CYP3A inducers should be avoided. Interactions may require additional monitoring, dose or frequency adjustment, and/or selection of alternative therapy.15

Sonidegib may cause embryo–fetal toxicity, for which a black box warning is included. Teratogenic effects were observed in animals. The manufacturer of sonidegib maintains a pregnancy registry. Table 4 provides more detail on use of sonidegib in pregnancy and lactation. Male patients should not donate sperm during treatment and for at least 8 months after the last dose.15

Sonidegib is designated as a hazardous agent, and appropriate precautions for handling and disposal should be considered. Sonidegib is the second available Hedgehog pathway inhibitor, providing another option for the treatment of locally advanced BCC.

Rolapitant
Rolapitant (Varubi—Tesaro) is an antiemetic approved for the prevention of chemotherapy-induced nausea and vomiting (CINV). Similar to aprepitant and netupitant, rolapitant is a substance P/neurokinin-1 (NK-1) receptor antagonist used for delayed nausea and vomiting associated with initial and repeat courses of chemotherapy, including but not limited to highly emetogenic chemotherapy (HEC). Rolapitant should be given in combination with other antiemetic agents.18

Rolapitant prevents delayed CINV by selectively and competitively inhibiting the substance P/NK-1 receptor. Rolapitant is highly protein-bound (99.8%) and undergoes hepatic metabolism by CYP3A4 to form the major active metabolite M19. The half-life of rolapitant is approximately 7 days, with a time to peak of about 4 hours.18

Rolapitant should be administered orally 1 to 2 hours prior to chemotherapy on the first day of each cycle but no less than at 2-week intervals. See Table 2 for additional dosing information. No dosage adjustments in renal impairment are necessary. Use in hepatic impairment Child-Pugh Class C should be avoided.18

Efficacy of rolapitant was demonstrated in four studies: two in patients receiving cisplatin-based HEC and two in patients receiving moderately emetogenic chemotherapy. The two HEC studies are reviewed here. These randomized, double-blind, parallel-group, placebo-controlled studies randomized patients receiving a chemotherapy regimen including cisplatin of greater than 60 mg/m2 to either rolapitant, granisetron, and dexamethasone or control therapy (placebo, granisetron, and dexamethasone). The primary endpoint of both studies was complete response (CR), defined as no emetic episodes and no rescue medication.19

In the first study, results showed the CR rate in the delayed phase was higher in the rolapitant arm (72.7%) compared with the placebo group (58.4%). In the second study, there was a 70.1% CR in the rolapitant arm compared with 61.9% in the placebo arm.19

Rolapitant should be avoided in patients with severe hepatic impairment. If use cannot be avoided, patients should
be monitored for adverse reactions related to rolapitant. Rolapitant has an inhibitory effect on CYP2D6 that may persist for at least 7 days (or longer); therefore, increased plasma concentrations of certain CYP2D6 substrates may result in QT prolongation and torsades de pointes. Monitor patients for adverse reactions if concomitant use with CYP2D6 substrates with a narrow therapeutic index cannot be avoided. Concurrent use of thiortidazone with rolapitant is contraindicated because of QT prolongation and Torsades de pointes. Numerous drug interactions exist, including with strong CYP3A4 inducers (e.g., rifampin); use of drug should be avoided with these agents. Consult the product labeling for more information.18

The most common adverse effects in rolapitant clinical trials were decreased appetite (9%), neutropenia (7%–9%), dizziness (6%), hiccups (5%), dyspepsia (4%), stomatitis (4%), urinary tract infection (4%), abdominal pain (3%), and anemia (3%). It is important to note that study participants were receiving combination therapy with a 5-HT3 receptor antagonist and dexamethasone and that the frequency of adverse events with rolapitant alone are unknown.19

Table 4 provides details about use of rolapitant in during pregnancy and lactation.20 Rolapitant offers another option to prevent delayed CINV. The primary differences from aprepitant are the longer duration of action and the dosing regimen (two tabs prior to chemotherapy for rolapitant compared with a three-capule regimen spread out over 3 days for apreptiant). Rolapitant has not been compared head to head with apreptiant; thus, its place in therapy remains unclear. In addition, rolapitant is not approved for acute nausea and vomiting associated with cancer chemotherapy.

**Trifluridine/tipiracil**

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the United States. The overall lifetime risk of developing this type of cancer is about 1 in 21 (4.7%) for men and 1 in 23 (4.4%) for women. In 2016, 49,190 deaths are expected to occur from CRC.14,20

Trifluridine/tipiracil (Lonsurf—Taiho Oncology) is a combination of a nucleoside metabolic inhibitor (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil). The combination is indicated for the treatment of patients with metastatic CRC. More specifically, it is meant for patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy; an antivascular endothelial growth factor (VEGF) drug; and, if RAS wild-type, an anti-epidermal growth factor receptor (EGFR) therapy.21

Tipiracil is included in the combination to increase trifluridine concentrations. It does so by inhibiting its metabolism via thymidine phosphorylase. Trifluridine is primarily bound to human albumin (>96%), whereas protein binding of tipiracil is low (<8%). Trifluridine and tipiracil are not metabolized by CYP450 enzymes.21

Trifluridine/tipiracil has a very detailed dosing regimen. It is dosed on body surface area and given on 28-day cycles, with dose modifications based on complete blood cell counts. See Table 2 for more information. No dosage adjustments are necessary on the basis of age or hepatic impairment, although patients with moderate renal impairment (creatinine clearance rate of 30–59 mL/min) had a higher incidence of adverse events, dose delays, and reductions compared with patients with normal renal function. No dose adjustment is necessary to the starting dose; however, patients with moderate renal impairment may require dose modification for increased toxicity.21

Efficacy of trifluridine/tipiracil was evaluated in the RE COURSE trial, a randomized, double-blind, placebo-controlled study conducted in patients with previously treated metastatic CRC.22 A total of 800 patients were randomized 2:1 to receive oral trifluridine/tipiracil plus best supportive care or placebo. Patients included in the study had received prior treatment with at least two lines of standard chemotherapy for metastatic CRC. Patients received trifluridine/tipiracil or placebo orally twice daily after meals on days 1 through 5 and days 8 through 12 of each 28-day cycle. Patients continued until disease progression or unacceptable toxicity. The primary endpoint was overall survival. A statistically significant improvement was seen with trifluridine/tipiracil (7.1 mo) compared with placebo (5.3 mo).22 The time to disease progression was 2 months for trifluridine/tipiracil compared with 1.7 months for placebo.

No contraindications are listed in the label. Warnings and precautions include severe myelosuppression and embryo-fetal toxicity. Patients should have their complete blood counts obtained prior to and on day 15 of each cycle. The dose may be reduced or put on hold when deemed clinically appropriate. In addition, because fetal harm can occur, women should be advised about the potential risk to a fetus and advised not to breastfeed (Table 4).21

The most common adverse reactions (≥10%) are anemia, neutropenia, asthenia/fatigue, nausea, thrombocytopenia, decreased appetite, diarrhea, vomiting, abdominal pain, and pyrexia.21

No drug-interaction studies have been conducted.21 Serious neutropenia, thrombocytopenia, and anemia occurred more commonly in patients aged 65 years or older. Patients with moderate renal impairment may require dose modifications for increased toxicity.

Trifluridine/tipiracil provides another option for patients with treatment-refractory CRC.

**Daratumumab, ixazomib, and elotuzumab**

Multiple myeloma (MM) is a relatively uncommon cancer. In the United States, the lifetime risk of getting MM is 1 in 143 (0.7%).20 The American Cancer Society estimates that in 2016, approximately 30,330 new cases will be diagnosed (17,900 in men and 12,430 in women) and about 12,650 deaths will likely occur (6,430 in men and 6,220 in women).20

MM is a cancer of plasma cells in the bone marrow. Normal plasma cells produce antibodies and are important for...
immune function. In MM, overgrowth of these cells leads to bone pain, fractures, infections, anemia, and other sequelae. MM is slightly more common in males and almost twice as common among African Americans. The average age at diagnosis is 65 to 70 years.23

Treatment options for MM include watchful waiting (for asymptomatic or smoldering MM), chemotherapy, treatment with immunomodulatory agents, and hematopoietic cell transplantation (HCT). The disease is rarely cured; however, treatment can provide relief of symptoms, induce remission, and prolong life.23

Specific treatment varies depending on many factors, including risk stratification, comorbidities, reduction of tumor burden, and willingness to receive HCT. Overall, it is important to note that treatment follows a patient-centered approach to care. Guidelines recommend that all patients receive induction therapy.23 For most patients with standard risk, treatment with bortezomib, lenalidomide, and dexamethasone alone is acceptable.24 Triple therapy with this regimen is associated with greater toxicity; thus, dual therapy with lenalidomide and dexamethasone is recommended. Triple therapy with this regimen is associated with greater toxicity; thus, dual therapy with lenalidomide and dexamethasone alone is an acceptable alternative for patients who are frail.23

In 2015, four new agents were approved to treat MM.13 Panobinostat (Farydak—Novartis) was reviewed in Part 1 of this series. The other three agents are discussed in this article (Table 7).

Daratumumab (Darzalex—Janssen Biotech) is a human monoclonal antibody indicated for the treatment of patients with MM who have received at least three prior lines of therapy (including a proteasome inhibitor and an immunomodulatory agent) or who are double-refractory to both. The drug received FDA breakthrough designation. Daratumumab targets cluster of differentiation 38 (CD38), a glycoprotein highly expressed on the cell surface of myeloma cells. Upon binding to CD38, daratumumab inhibits the growth of tumor cells expressing CD38 and induces apoptosis.24

Daratumumab has a complicated dosing regimen, including weight-based dosing as an I.V. infusion given until disease progression, along with a premedication protocol with antipyretics, antihistamines, and corticosteroids (Table 2). No dosage adjustments are required in renal or mild hepatic impairment, but the drug has not been studied in moderate to severe hepatic impairment.24

Approval of daratumumab was based on two open-label, single-arm studies.25 The first study was a Phase I/II monotherapy dose-escalation trial in patients with relapsed or refractory multiple myeloma (RRMM). The second study was an open-label, single-arm, Phase II trial enrolling patients with relapsed MM who had received prior treatments, including proteasome inhibitors and immunomodulatory agents.25

The primary endpoint in both studies was ORR. In the first study, results for those 42 patients receiving the 16 mg/kg dosing showed an ORR of 36%, with a median duration of response of 6.9 months. Results from the second study showed an ORR of 29.2%, with a median duration of response of 7.4 months in 106 participants receiving daratumumab.25

Product labeling lists no contraindications; however, infusion reactions are an important warning and precaution. Daratumumab administration should be interrupted for infusion reactions of any severity. Daratumumab interferes with cross-matching and red blood cell antibody screening. The most common adverse reactions (≥20%) include infusion reactions, fatigue, nausea, back pain, pyrexia, cough, and upper respiratory tract infection.24

In terms of monitoring, patients should have complete blood cell counts as clinically necessary and watch for signs and symptoms of infusion reactions. There are no known significant drug interactions. Table 4 provides more detail on use of daratumumab in pregnancy and lactation.24

Ixazomib (Ninlara—Takeda) is a new agent approved for the treatment of MM, given in combination with lenalidomide and dexamethasone in patients who have received at least one prior therapy. Daratumumab administration should be interrupted for infusion reactions of any severity. Daratumumab interferes with cross-matching and red blood cell antibody screening. The most common adverse reactions (≥20%) include infusion reactions, fatigue, nausea, back pain, pyrexia, cough, and upper respiratory tract infection.24

Ixazomib is a reversible proteasome inhibitor. It preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome. Ixazomib induces apoptosis of MM cells upon binding to the proteasome.26

Ixazomib is 99% bound to plasma proteins and has a half-life of 9.5 days, which allows for weekly oral dosing. The recommended starting dose of 4 mg is taken orally on days 1, 8, and 15 of a 28-day cycle. See Table 2 for detailed dosing.26 The starting dose of ixazomib should be decreased in patients with severe renal impairment or end-stage renal disease (ESRD) and in those with moderate or severe hepatic impairment.26

Efficacy and safety of ixazomib in combination with lenalidomide and dexamethasone were evaluated in a randomized, double-blind, placebo-controlled, multicenter study in 722 patients with relapsed and/or refractory MM who had received at least one prior line of therapy.27 The patients were randomized (1:1) to receive either the combination of ixazomib, lenalidomide, and dexamethasone or the combination of placebo, lenalidomide, and dexamethasone until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS).27

Response was assessed every 4 weeks until disease progression. Median PFS was 20.6 months with ixazomib compared with 14.7 months in the placebo group. Additional benefits were conferred in patients with high-risk cytogenetics, who express certain genes with a more aggressive disease.27

Ixazomib has no listed contraindications. The dose of ixazomib should be adjusted as needed on the basis of adverse effects, warnings, and precautions. The most common adverse reactions (≥20%) are diarrhea, constipation, thrombocytopenia, peripheral neuropathy, nausea, peripheral edema, vomiting, and back pain. Listed warnings and precautions include thrombocytopenia, gastrointestinal toxicities, peripheral neuropathy and edema, cutaneous reactions, hepatotoxicity, and embryo-fetal toxicity.26 Corresponding monitoring of ixazomib includes

- Platelet counts at least monthly during treatment
- Severe diarrhea, constipation, nausea, and vomiting
- Symptoms of peripheral neuropathy
Table 7. Treatment of multiple myeloma

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Indication</th>
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<td>Daratumumab</td>
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<tr>
<td>Ixazomib</td>
<td>Ninlaro</td>
<td>Patients who have received at least one prior therapy to be given in combination with lenalidomide and dexamethasone</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>Empliciti</td>
<td>Patients who have received one to three prior therapies to be given in combination with lenalidomide and dexamethasone</td>
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</tbody>
</table>

Sources: Refs. 24, 26, 28.

The most common adverse reactions (≥20%) of elotuzumab are fatigue, diarrhea, pyrexia, constipation, cough, peripheral neuropathy, nasopharyngitis, upper respiratory tract infection, decreased appetite, and pneumonia.

Elotuzumab labeling lists no contraindications or drug interactions; however, warnings and precautions (as well as monitoring parameters) include the following:

- Infusion reactions: premedication is required. (Interrupt elotuzumab for Grade 2 or higher reaction, and permanently discontinue for severe reactions.)
- Infections: monitor for fever and other signs of infection.
- Second primary malignancies: higher incidences of other cancers were observed in an elotuzumab clinical trial.
- Hepatotoxicity: monitor liver function and stop therapy for suspected hepatotoxicity.
- Interference with determination of complete response: elotuzumab can interfere with assays used to monitor M-protein, which may affect the determination of complete response to therapy.

Table 4 provides more detail about use of elotuzumab in pregnancy and lactation. While there are no studies with elotuzumab in pregnant women to inform patients about the associated risks, elotuzumab must be administered in combination with lenalidomide and dexamethasone. Lenalidomide can cause embryo–fetal harm and is contraindicated for use in pregnancy. Breastfeeding is not recommended. Safety and efficacy have not been established in pediatric patients, and no differences in efficacy were observed in patients on the basis of age.

Elotuzumab is a first-in-class agent with a novel mechanism of action. It adds another treatment option for patients with MM who have not responded to initial treatment(s).

**New infectious disease agent: Daclatasvir**

Daclatasvir (Daklinza—Bristol-Myers Squibb) is a new agent approved for the treatment of chronic hepatitis C virus (HCV) genotype 3 infection in combination with sofosbuvir. Daclatasvir is a direct-acting antiviral agent that inhibits its nonstructural protein 5A (NS5A). In the United States, approximately 10% to 12% of patients with hepatitis C have genotype 3 infection.

Daclatasvir is dosed 60 mg orally once daily with or without food in combination with sofosbuvir for a duration of 12 weeks. When used with strong CYP3A inhibitors, the dose should be reduced to 30 mg once daily. Conversely, given concomitantly with moderate CYP3A inducers, the dose should be increased to 90 mg once daily. Table 2 provides...
Efficacy and safety of daclatasvir were evaluated in the Phase III ALLY-3 trial. This open-label trial included 152 patients with chronic HCV genotype 3 infection and compensated liver disease. Two-thirds of the participants were treatment-naive (n = 101), with the remaining one-third being treatment-experienced (n = 51). Prior treatment with combination peginterferon/ribavirin had failed with the majority of treatment-experienced patients. The patients were also stratified by presence or absence of cirrhosis. The primary measure of efficacy in the study was rate of sustained virologic response (SVR). Results showed an SVR rate of 89% for all patients, with a 90% SVR in treatment-naive patients compared with an 86% SVR in treatment-experienced patients. Participants without cirrhosis had significantly better SVR rates than those with cirrhosis (96% vs. 63%).

Contraindications to use of daclatasvir include concomitant use with strong inducers of CYP3A (i.e., phenytoin, carbamazepine, rifampin, and St. John’s wort). Patients should be warned that serious symptomatic bradycardia might occur when daclatasvir is coadministered with sofosbuvir and amiodarone in combination. Other drug interactions include digoxin and dabigatran.

The most common adverse reactions (≥10%) observed with daclatasvir in combination with sofosbuvir were headache and fatigue. Embryo–fetal toxicity was observed in rats and rabbits; however, no data exist about risk in humans (Table 4).

Safety was similar across all age groups; however, safety in pediatric patients (≤18 y) has not been established. No dosage adjustment is required for patients with renal impairment or hepatic impairment, although patients with decompensated cirrhosis have not been studied.

The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America currently recommend daclatasvir in combination with sofosbuvir for 12 weeks in treatment-naive patients without cirrhosis. In patients with cirrhosis, current guidelines recommend 24 weeks of treatment with or without ribavirin.

As with the PCSK9 inhibitors, the cost of treating hepatitis C patients with these highly efficacious yet expensive drugs is a real concern.

**New rare-disease agent: Uridine triacetate**

Of the new drugs approved by FDA in 2015, 47% (21 of 45) were approved to treat rare or “orphan” diseases that affect fewer than 200,000 Americans. Patients with rare diseases often have no or few drugs available to treat their condition.

Uridine triacetate (Xuriden—Wellstat Therapeutics) is a new drug approved for a rare disease known as hereditary orotic aciduria. Orotic acid is an intermediate product produced in the pathway of pyrimidine synthesis. Patients with this disorder are unable to convert orotic acid to uridine, which is an essential component of RNA. Orotic aciduria results from excessive amounts of orotic acid in the urine (approximately 500 to 1,000 times the normal amount).

Administration of uridine triacetate is effective because it is converted into a form that is readily usable by the body for RNA formation. Uridine triacetate delivers fourfold to sixfold greater uridine systemically compared with equimolar doses of uridine itself. Maximum concentrations are generally achieved within 2 to 3 hours, with the drug’s half-life ranging from approximately 2 to 2.5 hours.

Hereditary orotic aciduria is a rare autosomal recessive disorder that leads to failure to thrive, cognitive deficits, growth retardation, megaloblastic anemia not corrected by folic acid and vitamin B12, immunodeficiency, and orotic aciduria.

Uridine triacetate is available in oral granules (two-gram packets that amount to three-quarters of a teaspoon). Dosing is weight-based, with the drug given orally once daily. See Table 2 for detailed dosing. Uridine triacetate may be administered with milk, formula, or soft food (e.g., applesauce, pudding, or yogurt). The recommended dose is 60 mg/kg/d. The dose may be titrated upward to 120 mg/kg/d if urinary orotic acid levels remain above normal or increase above the usual or expected range for the patient. Lab values show evidence of disease worsening, or there is worsening of other signs/symptoms of the disease. A complete dosing chart, including instructions for administration, can be found in the product labeling.

Efficacy and safety of uridine triacetate were evaluated in one open-label study involving four patients, as well as in a retrospective review of the clinical course of 18 patients with hereditary orotic aciduria who were treated with the agent beginning at ages 2 months to 12 years. Although data is unlimited, adults and pediatric patients appeared to have similar clinical response when treated with uridine triacetate. Clinical response was measured by the primary endpoint of hematologic parameters, with secondary endpoints including levels of orotic acid in the urine and height/weight.

The product label mentions no contraindications or warnings/precautions, and no adverse reactions have been reported. Drug interactions include the potential for uridine triacetate to interact with orally administered P-glycoprotein substrate drugs. Refer to Table 4 for pregnancy and lactation information.

Uridine triacetate received orphan drug status and expedited review to help meet the needs of patients with hereditary orotic aciduria.

**Other new agents**

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

**References**

### Table 8. Additional approvals of therapeutic agents

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Trade name</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>What’s new?</th>
</tr>
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<tbody>
<tr>
<td>Chlorpheniramine/codeine</td>
<td>Tuxarin ER</td>
<td>Spiraoso, Nexgen Pharma</td>
<td>Relief of cough and symptoms associated with upper respiratory allergies or the common cold</td>
<td>New combination</td>
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<td>Aspirin, controlled-release</td>
<td>Durlaza</td>
<td>New Haven</td>
<td>Once-daily, controlled-release formulation of aspirin for secondary prevention of stroke and acute cardiac events; oral therapy</td>
<td>New formulation</td>
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<td>Zolmitriptan</td>
<td>Zomig</td>
<td>Impax</td>
<td>Treatment of acute migraine headaches in patients aged 12–18 years</td>
<td>New indication in pediatric patients</td>
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<td>Aripiprazole lauroxil</td>
<td>Aristada</td>
<td>Alkermes</td>
<td>Treatment of schizophrenia</td>
<td>New I.M. formulation</td>
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<td>Calcipotriene/betamethasone dipropionate</td>
<td>Enstilar</td>
<td>Leo Pharma</td>
<td>Topical treatment of plaque psoriasis in patients aged 18 years and older</td>
<td>New topical dosage form</td>
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<td>Tris Pharma</td>
<td>Treatment of ADHD</td>
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<td>Veitassa</td>
<td>Relypsa</td>
<td>Treatment of hyperkalemia</td>
<td>New molecular entity</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Vivodex</td>
<td>Iroko Pharmaceuticals</td>
<td>Nonsteroidal anti-inflammatory drug indicated for management of osteoarthritis pain</td>
<td>New capsule dosage form</td>
</tr>
<tr>
<td>Buprenorphine hydrochloride</td>
<td>Belbuca</td>
<td>Endo Pharmaceuticals</td>
<td>Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate</td>
<td>New dosage form</td>
</tr>
<tr>
<td>Glycopyrrolate</td>
<td>Seebri</td>
<td>Novartis</td>
<td>Anticholinergic indicated for the long-term, maintenance treatment of airflow obstruction in patients with COPD</td>
<td>New powder inhalation dosage form</td>
</tr>
<tr>
<td>Glycopyrrolate; indacaterol maleate</td>
<td>Utibron</td>
<td>Novartis</td>
<td>Long-term, maintenance treatment of airflow obstruction in patients with COPD</td>
<td>New combination</td>
</tr>
<tr>
<td>Elvitegravir; cobicistat; emtricitabine; and tenofovir alafenamide</td>
<td>Genvoya</td>
<td>Gilead Sciences</td>
<td>Four-drug combination tablet indicated for the treatment of HIV-1 infection in patients aged 12 years and older</td>
<td>New combination</td>
</tr>
<tr>
<td>Halobetasol propionate</td>
<td>Ultravate</td>
<td>Ferndale Labs</td>
<td>Topical treatment of plaque psoriasis in patients aged 18 years and older</td>
<td>New dosage form</td>
</tr>
<tr>
<td>Naloxone hydrochloride</td>
<td>Narcan</td>
<td>Adapt Pharma</td>
<td>Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression</td>
<td>New dosage form</td>
</tr>
</tbody>
</table>

Abbreviations used: ER, extended release; COPD, chronic obstructive pulmonary disease.

2. Sacubitril/valsartan [prescribing information]. East Hanover, NJ: Novartis; August 2015.
16. Von Hoff DD, LoRusso PM, Rudin CM, et al. Inhibition of the Hedge-


18. Rolapitant [prescribing information]. Waltham, MA: Tesaro Inc; September 2015.


27. Moreau P, Masszi T, Grzasko N, et al. Ixazomib, an investigational oral proteasome inhibitor (PI), in combination with lenalidomide and dexamethasone (Rd), significantly extends progression-free survival (PFS) for patients (Pts) with relapsed and/or refractory multiple myeloma (RRMM): the phase 3 Tourmaline-MM study (NCT01564537). Blood. 2015;126(23):727.


CPE assessment
This assessment must be taken online; please see “CPE information” for further instructions. The online system will present these questions in random order to help reinforce the learning opportunity. There is only one correct answer to each question.

1. Which medication binds to substance P/N-K1 receptors?
   a. Uridine triacetate
   b. Trifluridine/tipiracil
   c. Daclatasvir
   d. Rolapitant

2. How does evolocumab differ from alirocumab?
   a. It is dosed more frequently than alirocumab.
   b. It is indicated for both heterozygous and homozygous familial hypercholesterolemia.
   c. It has a different route of administration than alirocumab.
   d. It has a different mechanism of action than alirocumab.

3. Which of the following drug : indication pairings is correct?
   a. Sacubitril/valsartan : chronic heart failure
   b. Ixazomib : metastatic colorectal cancer
   c. Daclatasvir : HIV infection
   d. Alirocumab : multiple myeloma

4. Which of the following drugs is administered subcutaneously?
   a. Sacubitril/valsartan
   b. Rolapitant
   c. Alirocumab
   d. Daratumumab

5. Which of the following statements is correct?
   a. Uridine triacetate was given orphan drug status for hereditary orotic aciduria.
   b. Daratumumab is a reversible proteasome inhibitor.
   c. Rolapitant may cause fetal toxicity.
   d. Trifluridine/tipiracil is indicated for locally advanced basal cell carcinoma.

6. Which of these agents is an NS5A inhibitor?
   a. Uridine triacetate
   b. Rolapitant
   c. Trifluridine/tipiracil
   d. Daclatasvir

7. Which of the following statements is correct about sacubitril/valsartan?
   a. It should be taken on an empty stomach.
   b. It is safe in breastfeeding.
   c. It should be discontinued immediately once pregnancy is detected.
   d. It is dosed once daily.

8. Which of the following statements is correct about sacubitril/valsartan?
   a. It does not have a risk of hypotension.
   b. The initial dose should be doubled as tolerated after 2 to 4 weeks.
   c. Concomitant use with aliskiren is preferred.
   d. It has no effect on kidney function.

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 March 1, 2019, 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.

CPE instructions
1. Log in or create an account at pharmacist.com, and select LEARN from the top of the page; select Continuing Education, then Home Study CPE to access the Library.
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 and evaluation.
4. To get your statement of credit, click Claim on the right side of the page. You will need to provide your NABP e-profile ID number to obtain and print your statement of credit.

Assistance is available Monday through Friday from 8:30 am to 5:00 pm ET at APhA Member Services at 800-237-APhA (2742) or by e-mailing education@aphanet.com.
9. Which of the following statements is correct about alirocumab?
   a. Initial dosing is 75 mg subcutaneously once every 2 weeks.
   b. It is given as three 25-mg injections consecutively within 30 minutes.
   c. It has significant risk for nasopharyngitis.
   d. It contains human protein.

10. Which of the following statements is correct about evolocumab?
    a. It has significant risk for diarrhea.
    b. It is safe to use in pregnancy.
    c. It may be dosed 140 mg subcutaneously every 2 weeks or 420 mg once monthly.
    d. Its dosing may be increased if the LDL-C response is inadequate.

11. Which of the following statements is correct about sonidegib?
    a. It is indicated for locally advanced basal cell carcinoma.
    b. It is administered intravenously.
    c. It should be taken with food.
    d. It may cause significant hypersensitivity reactions.

12. Which of the following statements is correct about rolapitant?
    a. It has no listed contraindications.
    b. It must be taken on an empty stomach.
    c. It must be given in combination with dexamethasone and a 5-HT3 antagonist.
    d. It should be dose adjusted in renal impairment.

13. Which of the following statements is correct about rolapitant?
    a. It has a shorter duration of action than aprepitant.
    b. It is not indicated for prevention of delayed chemotherapy-induced nausea and vomiting.
    c. It has no known drug interactions.
    d. It undergoes hepatic metabolism.

14. Which of the following statements is correct about uridine triacetate?
    a. It is contraindicated in pediatrics.
    b. The most common adverse effects include dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, and fatigue.
    c. It may be administered with milk, formula, or soft food.
    d. It is the prodrug of thymidine.

15. Which of the following statements is correct about trifluridine/tipiracil?
    a. It must be taken within 1 hour after morning and evening meals.
    b. It was approved for initial treatment of colorectal cancer.
    c. It has weight-based dosing and is given in weekly cycles.
    d. It is safe for use in pregnancy.

16. Which of the following statements is correct about daratumumab?
    a. It should be dose-adjusted based on renal function.
    b. Before receiving daratumumab, patients should be premedicated with rolapitant.
    c. It inhibits CD38 expression on tumor cells.
    d. It is indicated for treatment-naive patients with multiple myeloma.

17. Which of the following statements is correct about ixazomib?
    a. It is an irreversible proteasome inhibitor.
    b. It is safe for use during pregnancy.
    c. The most common adverse effects include injection site edema/swelling, hematoma, pain, numbness, and erythema.
    d. It must be used in combination with lenalidomide and dexamethasone.

18. Which of the following statements is correct about elotuzumab?
    a. It does not increase the risk of hepatotoxicity.
    b. It is safe for use in pediatric patients.
    c. It targets the SLAMF7 protein.
    d. It may be used as monotherapy.

19. Which of the following statements is correct about daclatasvir?
    a. It requires no dose adjustments when taken with CYP3A inhibitors.
    b. It may be used as monotherapy without sofosbuvir.
    c. It must be dose-adjusted in renal impairment.
    d. It is approved for the treatment of chronic HCV genotype 3.

20. Which of the following is administered intravenously?
    a. Daratumumab
    b. Ixazomib
    c. Sonidegib
    d. Uridine triacetate