NEW DRUGS

Sacubitril/valsartan, ivabradine hydrochloride, alirocumab, and evolocumab
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Agents for heart failure

Heart failure affects about 5 million people in the United States and is a leading cause of disability and death. The most common underlying causes of heart failure are hypertension, coronary heart disease, and myocardial infarction. Treatment of patients with symptomatic heart failure has most often included an angiotensin-converting enzyme (ACE) inhibitor (e.g., enalapril), a beta-adrenergic blocker (e.g., carvedilol, metoprolol), an aldosterone antagonist (i.e., spironolactone, eplerenone), and/or a diuretic (e.g., furosemide). An angiotensin receptor blocker (ARB; e.g., valsartan) is commonly used as an alternative to an ACE inhibitor.

Sacubitril/valsartan (Entresto—Novartis) is a complex comprising anionic forms of sacubitril and valsartan, sodium cations, and water molecules that dissociates into sacubitril and valsartan following oral administration. The new agent sacubitril is a prodrug that is rapidly converted by esterases to LBQ657, its active metabolite with a unique mechanism of action as a neprilisin inhibitor. Neprilisin is a neutral endopeptidase that causes degradation of certain vasoactive peptides such as natriuretic peptides and bradykinin. By inhibiting neprilisin, sacubitril/LBQ657 increases the concentrations of these peptides, thereby reducing vasoconstriction and sodium retention. Valsartan contributes to the cardiovascular and renal benefits of the new combination in patients with heart failure by inhibiting the actions of angiotensin II by selectively blocking AT₁ receptors.

Sacubitril has been evaluated and is supplied as part of a combination formulation with valsartan; it is not available as a single agent. The combination is specifically indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (New York Heart Association [NYHA] class II–IV) and reduced ejection fraction. It is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

The greater effectiveness of sacubitril/valsartan was evaluated in a clinical study involving more than 8,400 patients with symptomatic chronic heart failure and a left ventricular ejection fraction of 40% or lower. Patients had to have been previously treated with an ACE inhibitor or ARB for at least 4 weeks and on a maximally tolerated dose of a beta blocker. In addition to a beta blocker, most patients were also being treated with a diuretic and an aldosterone antagonist.

The new combination was compared with enalapril and determined to be superior to the latter agent in reducing the risk of the combined endpoint of cardiovascular death or hospitalization for heart failure (21.8% vs. 26.5%, respectively). Compared with enalapril, there was a significantly reduced rate of cardiovascular death (13.3% vs. 16.5%), hospitalizations related to heart failure (12.8% vs. 15.6%), and all-cause mortality (17% vs. 19.8%). The greater effectiveness of sacubitril/valsartan provides a significant advantage that will result in its first-line use as an alternative to an ACE inhibitor or ARB in regimens for the treatment of heart failure.

Sacubitril/valsartan may cause angioedema, and its use is contraindicated in patients with a history of angioedema related to previous treatment with an ACE inhibitor or ARB. Because of an increased risk of angioedema, the concurrent use of the new combination with an ACE inhibitor is also contraindicated, and it should not be administered within 36 hours of switching from or to an ACE inhibitor. One of the components (valsartan) of the sacubitril/valsartan formulation is an ARB, and concurrent use of another ARB should be avoided. In the clinical study, 0.5% of the patients treated with sacubitril/valsartan and 0.2% of the patients treated with enalapril experienced angioedema. There was a higher incidence of angioedema in black patients (2.4%) than in non-black patients. The concurrent use of sacubitril/valsartan with the direct renin inhibitor aliskiren (Tekturna—Novartis) is contraindicated in patients with diabetes, and concurrent use should be avoided in patients with renal impairment (estimated glomerular filtration rate [eGFR] less than 60 mL/min/1.73 m²).

The adverse events most often reported in the clinical study of sacubitril/valsartan include hypotension (18%), hyperkalemia (12%), cough (9%), dizziness (6%), and renal failure/acute renal failure (5%). In the patients treated with enalapril, hyperkalemia (14%) and cough (13%) were experienced more frequently. Patients being treated with high doses of diuretics are at greater risk of hypotension, and volume or salt depletion should be corrected prior to treatment with sacubitril/valsartan, or treatment should be initiated with a lower dosage. Serum
potassium concentrations should be monitored periodically, especially in patients with risk factors for hyperkalemia, such as severe renal impairment, diabetes, hypokaliemic–hyperaldosteronism, a high potassium diet, or concurrent use of a potassium-sparing diuretic (e.g., spironolactone), potassium supplement, or salt substitute containing potassium. Use of an ACE inhibitor or an ARB (including sacubitril/valsartan) may reduce renal function in susceptible individuals as a consequence of inhibiting the renin–angiotensin–aldosterone system. Renal function should be monitored in patients with renal artery stenosis, as well as in patients who develop a clinically significant decrease in renal function.

ACE inhibitors and ARBs may cause embryo-fetal harm if administered during pregnancy, with the risk of harm being greater during the second and third trimesters. This is the subject of a boxed warning in the labeling for sacubitril/valsartan. When pregnancy is determined, treatment should be discontinued as soon as possible, and a safer alternative treatment initiated. Although it is not known whether sacubitril and valsartan are excreted in human milk, breastfeeding is not recommended during treatment with the new combination.

In older adult patients, those who are volume-depleted, or those who have compromised renal function, the concurrent use of a nonsteroidal anti-inflammatory drug with sacubitril/valsartan may result in a worsening of renal function, and this risk should be periodically monitored. There have been reports of increased serum lithium concentrations and lithium toxicity in some patients treated concurrently with an ARB, and serum lithium concentrations should be monitored in patients also being treated with sacubitril/valsartan.

The systemic exposures of sacubitril, LBQ657, and valsartan are not altered to a clinically significant extent when administered with food, and the combination may be administered with or without food. Sacubitril is readily converted to LBQ657, but this active metabolite is not further metabolized to a significant extent. Valsartan is metabolized to only a limited extent. Most of a dose of sacubitril and its metabolite is excreted in the urine, whereas almost all of a dose of valsartan is excreted in the feces. The dosage of sacubitril/valsartan should be reduced in patients with severe renal impairment or moderate hepatic impairment. The new product has not been studied in patients with severe hepatic impairment, and it is not recommended for use in these patients.

The valsartan in the sacubitril/valsartan combination formulation is more bioavailable than the valsartan in other marketed formulations (e.g., Diovan—Novartis). An amount of 26 mg of valsartan in the combination product is equivalent to 40 mg of valsartan in other marketed tablet formulations. Sacubitril/valsartan film-coated tablets are supplied in 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg potencies. The recommended initial dosage is 49 mg/51 mg twice a day. After 2 to 4 weeks of treatment, the dosage should be increased to the target maintenance dosage of 97 mg/103 mg twice a day, as tolerated by the patient. A reduced initial dosage of 24 mg/26 mg twice a day is recommended in patients with moderate hepatic impairment and severe renal impairment (eGFR <30 mL/min/1.73 m²), as well as in patients not currently taking an ACE inhibitor or ARB or those previously being treated with a low dosage of one of these agents. In these patients, the dosage should be doubled every 2 to 4 weeks to the target maintenance dosage of 97 mg/103 mg twice a day, as tolerated by the patient. In patients being switched from an ACE inhibitor to sacubitril/valsartan, a washout period of 36 hours should separate the administration of the two products.

Ivabradine hydrochloride (Corlanor—Amgen) was also marketed in 2015 for the treatment of patients with heart failure. It causes a dose-dependent reduction in heart rate by blocking the hyperpolarization-activated cyclic nucleotide-gated channel responsible for the cardiac pacemaker I_f current, which regulates heart rate. The selective inhibition of the I_f current reduces the spontaneous pacemaker activity of the cardiac sinus node, resulting in a reduction in heart rate. Its use has not been associated with changes in ventricular repolarization or myocardial contractility.

Ivabradine is specifically indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction of 35% or lower who are in sinus rhythm with resting heart rate of at least 70 beats per minute and are either on maximally tolerated doses of beta blockers or have a contraindication to beta blocker use.

The effectiveness of ivabradine was evaluated in several large placebo-controlled studies. The study that provided the strongest support for its approval included patients with stable NYHA class II–IV heart failure who were receiving an optimized and stable clinical regimen that included maximally tolerated doses of beta blockers and, in most cases, an ACE inhibitor or ARB, spironolactone, and diuretics. The primary endpoint was a composite of the first occurrence of either hospitalization for worsening heart failure or cardiovascular death. Although ivabradine reduced the risk of the combined endpoint (25% vs. 29% of those receiving placebo), the benefit of the medication reflected only a reduction in the risk of hospitalization, with no favorable effect on the mortality component of the primary endpoint. In two other studies with a similar primary composite endpoint, ivabradine did not
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Use of ivabradine is contraindicated in patients with acute decompensated heart failure, blood pressure less than 90/50 mmHg, resting heart rate less than 60 bpm prior to treatment, and pacemaker dependence (heart rate maintained exclusively by the pacemaker). It is also contraindicated in patients with sick sinus syndrome, sinoatrial block, or third-degree atrioventricular (AV) block, unless a functioning demand pacemaker is present. In addition, its use should be avoided in patients with second-degree AV block, unless a functioning demand pacemaker is present.

Adverse events reported most often in the clinical study of ivabradine include bradycardia (10%), hypertension (9%), and atrial fibrillation (8%). Patients should be advised to report significant decreases in heart rate or symptoms such as dizziness, fatigue, or hypotension, as well as symptoms of atrial fibrillation such as heart palpitations, chest pressure, or worsened shortness of breath.

Approximately 3% of patients experienced luminous phenomena, also designated as phosphenes, which are characterized by a transiently enhanced brightness in a limited area of the visual field, and effects such as halos, kaleidoscopic effects, colored bright lights, or multiple images. The retinal current $I_n$ is involved in reducing retinal responses to bright light stimuli, and the occurrence of phosphenes is thought to result from ivabradine’s action to inhibit this current. Onset of visual disturbances is generally within the first 2 months of treatment, after which they may occur repeatedly.

Ivabradine may cause harm to the unborn child if it is used during pregnancy, and women of childbearing potential should be advised to use effective contraception. Although it is not known whether ivabradine is excreted in human milk, breastfeeding is not recommended during treatment.

Ivabradine undergoes first-pass elimination in the gastrointestinal tract and liver, and its absolute oral bioavailability is approximately 40%. Food increases plasma exposure, and the drug should be administered with food. It is metabolized primarily via cytochrome P450 (CYP) 3A4–mediated oxidation, and its major metabolite is equipotent to the parent compound. This active metabolite circulates at concentrations approximately 40% of those of ivabradine and is also metabolized by CYP3A4. Less than 5% of a dose of ivabradine is excreted unchanged in the urine, and excretion of metabolites occurs to a similar extent via feces and urine. Dosage adjustment is not necessary in patients with impaired renal function (creatinine clearance of 15–60 mL/min), but the drug has not been studied in patients with a creatinine clearance below 15 mL/min. It is not necessary to adjust the dosage in patients with mild or moderate hepatic impairment. However, an increase in systemic exposure is anticipated in patients with severe hepatic impairment, and ivabradine is contraindicated in these patients.

Strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole) may increase the concentration and risk of exacerbation of bradycardia and conduction disturbances of ivabradine, and concurrent use is contraindicated. Concurrent use of ivabradine and a moderate CYP3A4 inhibitor (e.g., diltiazem, verapamil, grapefruit juice) should be avoided. In addition to increasing ivabradine exposure, diltiazem and verapamil may themselves contribute to reduction of heart rate. CYP3A4 inducers (e.g., carbamazepine, rifampin, St. John’s wort) may reduce the action of ivabradine, and concurrent use should be avoided.

The risk of bradycardia is increased by the concurrent use of ivabradine with other drugs that slow heart rate, such as diltiazem, verapamil, digoxin, and amiodarone. Heart rate should be closely monitored in patients taking these medications. Although beta blockers also slow heart rate, their benefits in patients with heart failure result in their use in most patients who are candidates for the addition of ivabradine to the treatment regimen.

Dosing of ivabradine is based on heart rate reduction, targeting a heart rate of 50 to 60 bpm. Some patients have a demand pacemaker set to a rate of 60 bpm or higher, and they cannot achieve a target heart rate of less than 60 bpm. These patients were excluded from the clinical studies, and ivabradine is not recommended for use in patients with pacemakers set at this rate.

The recommended initial dosage of ivabradine is 5 mg twice a day with meals. The patient should be assessed after 2 weeks of treatment, and the dosage should be adjusted to achieve a resting heart rate of 50 to 60 bpm. Thereafter, the dosage should be adjusted based on resting heart rate and tolerability. The maximum dosage is 7.5 mg twice a day. In patients with a history of conduction defects, or other patients in whom bradycardia could lead to hemodynamic compromise, treatment should be initiated with a dosage of 2.5 mg twice a day and subsequently increased, as appropriate, based on heart rate.

Ivabradine hydrochloride is supplied in film-coated tablets in amounts equivalent to 5 mg and 7.5 mg of ivabradine. The tablets are scored and can be divided in halves to provide a dose of 2.5 mg.

**Lipid-regulating agents**

Familial hypercholesterolemia is an inherited condition that is associated with high concentrations of low-density lipoprotein cholesterol (LDL-C). High concentrations of LDL-C are linked to the occurrence of heart disease, the number one cause of death in the United States, from which more than 600,000 Americans die every year. The
statins (e.g., atorvastatin) have been highly effective and widely prescribed as the standard of therapy for reducing elevated LDL-C concentrations and the related risks of cardiovascular disease. However, some patients who are treated with a maximally tolerated dose of a statin still require additional lowering of LDL-C.

Proprotein convertase subtilisin kexin type 9 (PCSK9) is a protein that binds to the low-density lipoprotein receptors (LDLRs) on the surface of hepatocytes to promote LDLR degradation in the liver. Because LDLR is the primary receptor that clears circulating LDL, a decrease in LDLR by PCSK9 results in higher blood concentrations of LDL-C. In mid-2015, the U.S. Food and Drug Administration approved two human monoclonal antibodies that target PCSK9 and inhibit its activity. Alirocumab (Praluent—Regeneron; Sanofi) was the first PCSK9 inhibitor to be approved. Approximately 1 month later, evolocumab (Repatha—Amgen) became the second drug to be approved in this new class of agents. By inhibiting the binding of PCSK9 to LDLR, the new drugs increase the number of LDLRs available to clear LDL, thereby lowering LDL-C concentrations.

Both alirocumab and evolocumab are administered subcutaneously and are indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (CVD) who require additional lowering of LDL-C. Evolocumab is also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

The addition of either of the new drugs to the regimen resulted in a substantial further reduction in LDL-C concentrations compared with placebo, and treatment regimens including the new drugs are more effective than other regimens in reducing LDL-C concentrations. Thus, the new agents represent important additions to the options available for reducing LDL-C concentrations. Although the statins have been demonstrated to reduce the risk of having a heart attack or stroke, the effects of alirocumab and evolocumab on cardiovascular morbidity and mortality have not been determined.

The cost of alirocumab and evolocumab is approximately $14,000 a year and has been the subject of extensive discussion and concern. Insurance companies and pharmacy benefit managers have implemented criteria to determine the eligibility of patients for coverage of these agents, and certain of these criteria have also been a source of concern.

Effectiveness of alirocumab was demonstrated in five placebo-controlled studies in patients who were already being treated with a maximally tolerated dosage of a statin, with or without other lipid-modifying therapy. Addition of alirocumab to the regimen resulted in a further lowering of LDL-C concentrations by approximately 50% compared with placebo.

Some patients have experienced hypersensitivity reactions with the use of alirocumab, including serious events that required hospitalization. Hypersensitivity reactions resulted in discontinuation of treatment in 0.6% of patients, compared with 0.2% of patients receiving placebo.

The most commonly experienced adverse events in the studies with alirocumab include nasopharyngitis (11%), injection site reactions (7%), influenza (6%), urinary tract infection (5%), and diarrhea (5%), although the frequency of these events was only slightly higher than in individuals receiving placebo.

As with other therapeutic proteins, there is a potential for immunogenicity with alirocumab, and approximately 5% of patients developed antidrug antibodies (ADAs). Patients who developed ADAs had a higher incidence of injection site reactions compared with patients who did not develop ADAs. A total of 1.2% of patients who were treated with alirocumab developed neutralizing antibodies, and 0.3% of patients both tested positive for neutralizing antibodies and exhibited loss of efficacy.

Alirocumab has not caused adverse effects on the fetus in animal reproduction studies, but it has not been evaluated in pregnant women. Effectiveness and safety of the drug in pediatric patients have not been established.

Alirocumab is administered subcutaneously in the thigh, abdomen, or upper arm. The recommended starting dosage is 75 mg once every 2 weeks. If the LDL-C response is not adequate, the dosage may be increased to the maximum dosage of 150 mg once every 2 weeks. LDL-C concentrations should be determined within 4 to 8 weeks of initiating treatment or changing the dosage. If a dose is missed, the patient should administer the dose within 7 days of the missed dose and then resume the regular dosage schedule. If the missed dose is not administered within 7 days, the patient should wait until the next dose on the original schedule.

Alirocumab injection is supplied in single-dose, prefilled pens and syringes containing 75 mg and 150 mg of the drug. The products should be stored in a refrigerator. The injection should be allowed to warm to room temperature for 30 to 40 minutes prior to administration and should be administered as soon as possible after it has warmed up. The product should not be used if it has been at room temperature for 24 hours or longer.

In addition to the indications for which alirocumab has been approved, evolocumab is also indicated as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis)
for the treatment of patients with HoFH who require additional lowering of LDL-C. Effectiveness of evolocumab has been demonstrated in multiple placebo-controlled studies in patients with clinical atherosclerotic CVD or HeFH who were already being treated with a maximally tolerated dosage of a statin. Addition of evolocumab to the regimen resulted in a further lowering of LDL-C concentrations by approximately 60% compared with placebo. In patients with HoFH, evolocumab reduced LDL-C by approximately 30% compared with placebo.

The most commonly reported adverse events in the longest study (52 weeks) of evolocumab are generally similar in type and incidence to those experienced with alirocumab. They include nasopharyngitis (11%), upper respiratory tract infection (9%), influenza (8%), back pain (6%), injection site reactions (6%), urinary tract infection (5%), and cough (5%). Approximately 5% of the patients treated with evolocumab experienced hypersensitivity reactions (e.g., rash, eczema, erythema, urticaria), but these events did not usually necessitate discontinuation of treatment.

Like alirocumab and other therapeutic proteins, there is a potential for immunogenicity with evolocumab. However, only 0.1% of the patients tested positive for ADAs, and none of the patients tested positive for neutralizing antibodies.

Evolocumab has not caused adverse effects on pregnancy or neonatal/infant development in animal reproduction studies. However, it has not been evaluated in pregnant women. Effectiveness and safety of evolocumab in pediatric patients with HeFH or clinical atherosclerotic CVD, and in patients with HoFH who are younger than 13 years old, have not been established. The study in patients with HoFH included a small number of adolescents (aged 13–17) in whom effectiveness and safety were demonstrated.

Evolocumab is administered subcutaneously in the thigh, abdomen, or upper arm. The recommended dosage is 140 mg once every 2 weeks or 420 mg once a month in patients with HeFH or patients with primary hyperlipidemia with established clinical atherosclerotic CVD. To administer a dose of 420 mg, three injections of 140 mg should be administered consecutively within 30 minutes. Approval is being sought for a higher-potency formulation that would permit administration of the higher dose in one injection. In patients with HoFH, the recommended dosage is 420 mg once a month, and LDL-C concentrations should be measured 4 to 8 weeks after initiating treatment because responses to therapy will depend on the degree of LDL-receptor function.

If a dose is missed, the dose 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.

Evolocumab injection is supplied in single-use, prefilled auto-injectors and syringes containing 140 mg of the drug. The products should be stored in a refrigerator. The formulation should be allowed to warm to room temperature for at least 30 minutes prior to administration. Alternatively, the formulation may be kept at room temperature in the original carton but must be used within 30 days.

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