Drug and Biologic Coverage Policy

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Coverage Policy Number 1509

PCSK9 Inhibitors

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Coverage Policy

PCSK9 Inhibitors include:
- **Praluent®** (alirocumab)
- **Repatha®** (evolocumab)

Repatha (evolocumab)

Evolocumab (Repatha) is considered medically necessary for the treatment of hyperlipidemia in an adult (18 years or older) when ALL of the following criteria are met:

- **Individual has documentation of EITHER of the following:**
  - **Established clinical atherosclerotic cardiovascular disease (ASCVD) as evidenced by any of the following:**
    - Coronary heart disease (acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization)
    - Cerebrovascular disease (stroke, transient ischemic attack)
    - Peripheral arterial disease (PAD) of atherosclerotic origin
  - **Primary Hyperlipidemia (Including Heterozygous Familial Hypercholesterolemia) as defined by one of the following:**

- WHO Criteria (Dutch Lipid Network clinical criteria, score greater than 5; see Appendix 1)
- Simon-Broome Criteria (threshold met for "definite" or "possible" familial hypercholesterolemia, see Appendix 2)
- Confirmed genetic testing
- LDL-C ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents)
- Clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma)

- **ONE of the following:**
  - **Documented contraindication per FDA label to statin therapy**
  - **Documented intolerance to at least TWO statins with symptoms or abnormal lab results being temporally related to statin and other causes being ruled out**
  - **Inadequate response (LDL-C greater than 70 mg/dL) when ALL of the following criteria are met:**
    - Lipid lowering therapy with statins defined as **EITHER** of the following:
      - **High-intensity statin therapy** (atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day)
      - **Moderate intensity, or low intensity statin therapy** and documented intolerance to atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day
    - Statin therapy is used in combination with ezetimibe (Zetia) OR there is a contraindication per FDA label, documented intolerance, or the individual is not a candidate for ezetimibe (for example, LDL-C lowering to achieve target exceeds 15-20%)
    - Regimen has been taken for a minimum duration of 12 consecutive weeks

- **Use is adjunctive to diet and maximally tolerated statin therapy (unless contraindicated or intolerant)**

Evolocumab (Repatha) is considered medically necessary for the treatment of homozygous familial hypercholesterolemia (HoFH) in an individual 13 years of age or older when ALL of the following criteria are met:

- **Documented diagnosis of HoFH as demonstrated by EITHER of the following:**
  - Genetic confirmation of 2 mutant alleles at the LDL receptor, ApoB, PCSK9 or ARH adaptor protein gene locus
  - An untreated LDL-C greater than 500 mg/dL OR a total treated LDL-C greater than or equal to 300 mg/dL AND one of the following:
    - Cutaneous or tendinous xanthoma before the age of 10 years
    - Untreated LDL-C levels consistent with heterozygous familial hypercholesterolemia in both parents (greater than 190 mg/dL)

- **Inadequate response (LDL-C greater than 70 mg/dL) with maximally tolerated lipid lowering therapy regimen (for example, high-intensity statin, ezetimibe, LDL apheresis) AND use will be adjunctive to diet and maximally tolerated lipid lowering therapy (unless contraindicated or intolerant)**

- **Will not be used in combination with lomitapide (Juxtapid®)**

Praluent (alirocumab)

Alirocumab (Praluent) is considered medically necessary for the treatment of hyperlipidemia in an adult (18 years or older) when ALL of the following criteria are met:

- **Criteria listed above for evolocumab (Repatha) for the treatment of hyperlipidemia are met**
- **Either of the following:**
  - Not a candidate for evolocumab (Repatha) prefilled syringe or autoinjector due to documented latex sensitivity AND inability to use the Repatha on-body infusor
  - Documented intolerance to evolocumab (Repatha**)**

Initial authorization of alirocumab (Praluent) or evolocumab (Repatha) is up to 6 months

- For Repatha, the dose approved for ASCVD/HeFH is 140 mg every 2 weeks OR 420 mg monthly via Repatha Pushtronex
- The dose of Repatha approved for HoFH is 420 mg once monthly.

- For Praluent, the recommended starting dose of Praluent is 75 mg once every 2 weeks. An alternative starting dosage is 300 mg once every 4 weeks. For patients receiving Praluent 75 mg every 2 weeks, the dosage may be adjusted to the maximum dosage of 150 mg administered every 2 weeks. For patients receiving Praluent 300 mg every 4 weeks, the dosage may be adjusted to 150 mg every 2 weeks starting the new dose on the next scheduled dosing date.
- The recommended dose of Praluent in patients with HeFH undergoing LDL apheresis is 150 mg once every 2 weeks.

Alirocumab (Praluent) or evolocumab (Repatha) are considered medically necessary for continued use when BOTH of the following are met:

- Initial criteria listed above are met
- Documented evidence of clinical beneficial response (for example, demonstrated reduction of LDL-C)

Reauthorization is up to 12 months

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

The use of PCSK9 Inhibitors are considered experimental, investigational or unproven for ANY other use including the following:

- Use of PCSK9 inhibitors for individuals with 2 null LDLR pathogenic variants and/or LDL receptor activity less than 2%.
- Use of any PCSK9 Inhibitor to prevent cardiovascular events in patients **without** established cardiovascular disease
- Concurrent use of either alirocumab (Praluent) or evolocumab (Repatha) with each other or in combination with lomitapide (Juxtapid)

Note: Receipt of sample product does not satisfy any criteria requirements for coverage.

FDA Approved Indications

Drug	FDA Approved Indications
Praluent (alirocumab)	**Prevention of Cardiovascular Events** Praluent is indicated to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease. **Primary Hyperlipidemia (Including Heterozygous Familial Hypercholesterolemia)** Praluent is indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C).
Repatha (evolocumab)	**Prevention of Cardiovascular Events** In adults with established cardiovascular disease, Repatha is indicated to reduce the risk of myocardial infarction, stroke, and coronary revascularization. **Primary Hyperlipidemia (Including Heterozygous Familial Hypercholesterolemia)**

Drug	FDA Approved Indications
	Repatha is indicated as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia to reduce low-density lipoprotein cholesterol (LDL-C). **Homozygous Familial Hypercholesterolemia** Repatha is 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.

Recommended Dosing

Drug	FDA Recommended Dosing
Praluent (alirocumab)	The recommended starting dose of Praluent is 75 mg once every 2 weeks administered subcutaneously, since the majority of patients achieve sufficient LDL-C reduction with this dosage. An alternative starting dosage for patients who prefer less frequent dosing is 300 mg once every 4 weeks (monthly). For patients receiving Praluent 75 mg every 2 weeks, measure LDL-C levels within 4 to 8 weeks of initiating Praluent. If the LDL-C response is inadequate, the dosage may be adjusted to the maximum dosage of 150 mg administered every 2 weeks. Reassess LDL-C within 4 to 8 weeks. For patients receiving Praluent 300 mg every 4 weeks, measure LDL-C just prior to the next scheduled dose, since in some patients LDL-C can vary considerably between doses with this regimen. If LDL-C reduction is inadequate, the dosage may be adjusted to 150 mg every 2 weeks, starting the new dose on t>he next scheduled dosing date. Reassess LDL-C within 4 to 8 weeks. If an every-2-week dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule. If an every-4-week dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to administer the dose, starting a new schedule based on this date. The recommended dose of Praluent in patients with HeFH undergoing LDL apheresis is 150 mg once every 2 weeks. Praluent can be administered without regard to the timing of apheresis.
Repatha (evolocumab)	The recommended subcutaneous dosage of Repatha in adults with established cardiovascular disease or in adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) is either 140 mg every 2 weeks OR 420 mg once monthly, based on patient preference for dosing frequency and injection volume. When switching dosage regimens, administer the first dose of the new regimen on the next scheduled date of the prior regimen. The recommended subcutaneous dosage of Repatha in patients with HoFH is 420 mg once monthly. In patients with HoFH, measure LDL-C levels 4 to 8 weeks after starting Repatha, since response to therapy will depend on the degree of LDL-receptor function.

Drug	FDA Recommended Dosing
	When monitoring LDL-C for patients receiving Repatha 420 mg once monthly, note that LDL-C can vary considerably during the dosing interval in some patients [*see Clinical Studies*]. If a dose is missed, instruct the patient to administer Repatha within 7 days from the missed dose and resume the patient's original schedule. ▪ If an every-2-week dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule. ▪ If a once-monthly dose is not administered within 7 days, instruct the patient to administer the dose and start a new schedule based on this date.

Drug Availability

Drug	Drug Availability
Praluent (alirocumab)	Available for injection as single-dose pre-filled pens or syringes as 75 mg/mL or 150 mg/mL in packages of 1 pen or syringe or 2 pens or syringes.
Repatha (evolocumab)	Available for injection as a 140 mg/mL solution in a single-use prefilled syringe or SureClick® autoinjector in packages of 1 syringe or 1, 2, or 3 SureClick® autoinjectors. Also available as 420 mg/3.5 mL solution in a single-use Pushtronex™ system (on-body infusor with prefilled cartridge). Advise latex-sensitive patients that the following components contain dry natural rubber (a derivative of latex) that may cause allergic reactions in individuals sensitive to latex: the needle cover of the glass single-use prefilled syringe and the single-use prefilled autoinjector. The single-use on-body infusor with prefilled cartridge is NOT made with natural rubber latex.

General Background

Disease Overview

Elevated low-density lipoprotein cholesterol (LDL-C) is the primary target for treatment of hyperlipidemia as it is a major risk factor for coronary heart disease. The National Health and Nutrition Examination Survey (NHANES) data from 2005-2008 estimate that 71 million (33.5%) of U.S. adults (20 years of age and older) have a high LDL-C. NHANES data also indicates that only 48.1% were treated and 33.2% achieved LDL-C control (CDC, 2011). Familial hypercholesterolemia (FH) is characterized by very high LDL-C levels and early ASCVD (Jacobson, 2015). The incidence of homozygous FH is estimated as 1 in 1,000,000 and the incidence of heterozygous FH is estimated as 1 in 500 (Cuchel, 2014).

Lifestyle modifications (e.g., diet, exercise) are non-pharmacologic therapies for hyperlipidemia. Randomized clinical trials utilizing 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors or statin therapy have demonstrated reduction in atherosclerotic cardiovascular disease (ASCVD) events in primary and secondary prevention (Grundy, 2018).

The long-term persistence with statin therapy was addressed in a retrospective cohort study of over 34,000 individuals 65 years and older enrolled in a state Medicaid and pharmaceutical assistance programs. The proportion of days covered (PDC) was calculated based on the quantity dispensed and the number of days supplied from each prescription. A PDC of at least 80% was considered "adherent" to therapy. For the first 3 months of treatment, the PDC was 79%. At 6 months, the PDC dropped to 56% and was 50% after 12 months and 42% after 120 months. The authors concluded that persistence with statin treatment decreases over time with the greatest decline occurring during the first 6 months of therapy (Benner, 2002).

Pharmacology

PCSK9 (proprotein convertase subtilisin kexin type 9) leads to the degradation of low-density lipoprotein receptors (LDLR) in the liver. Inhibition of PCSK9 results in an increased number of LDLR to remove LDL, resulting in lower LDL-C levels.

Professional Societies/Organizations

Clinical practice guidelines recommend statins as the primary treatment modality for hyperlipidemia when LDL-C lowering therapy is indicated.

Many guidelines are available regarding the treatment of patients with dyslipidemia. Some of the guidelines have incorporated the PCSK9s but do not advocate the use of one product over another. Selected nationally-recognized guidelines are highlighted.

American Heart Association/American College of Cardiology/ (AHA/ACC)

In 2018 the AHA/ACC published a guideline on the management of blood cholesterol. Some key points that involved PCSK9 therapy are cited below.

- In patients with clinical ASCVD, reduce LDL-C with high-intensity statin therapy (atorvastatin 40 mg or 80 mg QD or rosuvastatin 20 mg or 40 mg QD).
- For patients with very high risk ASCVD, use a target of LDL-C ≥ 70 mg/dL to consider addition of nonstatins to statin therapy. In patients who are at very high risk whose LDL-C is ≥ 70 mg/dL on a maximally tolerated statin and ezetimibe, consider adding a PCSK9 inhibitor.
- In patients with severe primary hypercholesterolemia (LDL-C ≥ 190 mg/dL) begin high-intensity statin therapy. If the LDL-C level remains ≥ 100 mg/dL, the addition of ezetimibe is reasonable. If the LDL-C level with statins plus ezetimibe remains ≥ 100 mg/dL and the patient has multiple factors that increase the risk of ASCVD events, consider a PCSK9 inhibitor.

Table 1: High-, Moderate-, and Low-Intensity Statin Therapy (Grundy, 2018)

High-Intensity Statin Therapy	Moderate-Intensity Statin Therapy	Low-Intensity Statin Therapy
Daily dose lowers LDL-C, on average, by approximately > 50% Atorvastatin 40-80 mg Rosuvastatin 20-40 mg	Daily dose lowers LDL-C, on average, by approximately 30% to < 50% Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg BID Pitavastatin 2-4 mg	Daily dose lowers LDL-C, on average, by < 30% Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg

ACC – Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of ASCVD Risk.

In July 2016, the ACC published an expert consensus decision regarding the role of non-statin therapies, which included recommendations regarding PCSK9 inhibitors, including Repatha and Praluent (Lloyd, 2016). In 2017, a focused update was published to the 2016 ACC Expert Consensus decision pathway on the role of non-statin therapies for LDL-C lowering in the management of ASCVD (Lloyd, 2017). A summary of selected recommendations are below.

- For patients with stable clinical ASCVD without comorbidities, on statin for secondary prevention, the expert consensus writing committee supports considering of adding ezetimibe 10 mg daily as the initial non-statin agent, given the benefits on ASCVD outcomes and demonstrated safety of ezetimibe in patients with ACS treated with ezetimibe plus simvastatin vs. simvastatin monotherapy (Lloyd, 2016). In those who are on maximally-tolerated statin-ezetimibe, or non-statin combination therapy in the setting of documented statin intolerance and achieve a less than anticipated response with < 50% reduction in LDL-C, it is reasonable to engage in clinician-patient discussion with consideration of the net benefit of Praluent or Repatha (in addition or in place of ezetimibe) as a second step to achieve further LDL-C reduction.

- For patients with clinical ASCVD with comorbidities on statin for secondary prevention and baseline LDL-C of 70 to 189 mg/dL, if a decision is made to proceed with the addition of non-statin therapy to maximally-tolerated statin therapy in patients with clinical ASCVD with comorbidities and baseline LDL-C of 70 to 189 mg/dL, it is reasonable to consider the addition of either ezetimibe or a PCSK9 inhibitor based on considerations of the additional percent LDL-C reduction desired, patients preferences, route of administration, as well as other factors (Lloyd, 2017). Clinicians should preferentially prescribe agents that have been demonstrated to provide ASCVD risk-reduction benefits that outweigh the potential for AEs and drug-drug interactions, and consider patient preferences. Considerations that may favor the initial choice of ezetimibe include patients who require < 25% additional lowering of LDL-C, patients with ACS < 3 months, and recent availability of generic ezetimibe, ease of use as oral agent with low pill burden, patient preferences, heart failure, hypertension, age > 75 years, diabetes, stroke, coronary artery bypass grafting, PAD, estimated glomerular filtration rate < 60 mL/min/1.73m^2, and smoking. If patients with clinical ASCVD and comorbidities require > 25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial non-statin agent. The clinician-patient discussion should consider the extent of available scientific evidence for net ASCVD risk-reduction benefit, administration by SC injection, once every 14 day or QM dosing schedule, and storage requirements.
- For patients with clinical ASCVD and baseline LDL-C ≥ 190 mg/dL not due to secondary causes, on statin for secondary prevention (likely patients with HoFH and HeFH), it is reasonable to consider the addition of either ezetimibe or a PCSK9 inhibitor as the initial non-statin agent (Lloyd, 2017). Although there is a gap in the evidence regarding outcomes benefit of using ezetimibe plus statin therapy, the addition of ezetimibe 10 mg may be considered as the initial non-statin agent for patients in whom additional LDL-C lowering is desired. Considerations that may favor initial choice of ezetimibe include patients who require < 25% additional lowering of LDL-C, those with a recent ACS, ease of use with an oral agent and patient preferences. For patients with clinical ASCVD and baseline LDL-C ≥ 190 mg/dL who require > 25% lowering of LDL-C or who have additional comorbidities, a PCSK9 inhibitor may be preferred as the initial non-statin agent.

American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease.

In April 2017, the American Association of Clinical Endocrinologist and the American College of Endocrinology published guidelines for the management of dyslipidemia and prevention of CV disease (Jellinger, 2017). A summary of selected recommendations, mainly those that pertain to LDL-C goals, are below.

- For individuals at low ASCVD risk, (e.g., no risk factors), an LDL-C goal < 130 mg/dL is recommended.
- For individuals at moderate risk (i.e., those with two or fewer risk factors and a calculated 10-year risk of < 10%), an LDL-C goal < 100 mg/dL is recommended.
- For individuals at high risk (i.e., with an ASCVD equivalent including diabetes or stage 3 or 4 chronic kidney disease [CKD] with no other risk factors, or individuals with two or more risk factors and a 10-year risk of 10% to 20%), an LDL-C goal < 100 mg/dL is recommended.
- For individuals at very high risk (i.e., with established or recent hospitalization for ACS; coronary, carotid or peripheral vascular disease; diabetes or stage 3 or 4 CKD with one or more risk factors; a calculated 10-year risk > 20%; or HeFH), an LDL-C goal < 70 mg/dL is recommended).
- For individuals at extreme risk (i.e., with progressive ASCVD, including unstable angina that persists after achieving an LDL-C < 70 mg/dL, or established clinical ASCVD in individuals with diabetes, stage 3 or 4 CKD, and/or HeFH, or in individuals with a history of premature ASCVD [< 55 years of age or males < 65 years of age for females), an LDL-C goal < 55 mg/dL is recommended.
- HDL-C should be > 40 mg/dL, but also as high as possible mainly through the use of lifestyle interventions and if risk factors are present, through the use of pharmacotherapy mainly that focuses on reducing LDL-C.
- TG goals < 150 mg/dL are recommended.
- Regarding pharmacologic therapy, for patients at ASCVD risk aggressive lipid-modifying therapy is recommended to achieve appropriate LDL-C goals.
    - Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials.
    - For patients within high-risk and very high-risk categories, further LDL-C lowering beyond established targets with statins results in additional ASCVD event reduction and may be considered.
    - Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes who also have at least one additional risk factor should be treated with statins to target a reduced LDL-C treatment goal of < 70 mg/dL.

- Extreme-risk individuals should be treated with statins to target an even lower LDL-C treatment goal of < 55 mg/dL.
- Fibrates should be used to treat severe hypertriglyceridemia (TG > 500 mg/dL).
- Prescription omega-3 oil, 2 to 4 grams daily, should be used to treat severe hypertriglyceridemia (TG > 500 mg/dL). Dietary supplements are not FDA-approved for the treatment of hypertriglyceridemia and generally are not recommended for this purpose.
- Niacin therapy is recommended principally as an adjunct for reducing TG.
- Bile acid sequestrants may be considered for reducing LDL-C and apo B and modestly increasing HDL-C, but they may increase TG levels.
- Ezetimibe may be considered as monotherapy in reducing LDL-C and apo B, especially in statin-intolerant individuals. Ezetimibe may also be used in combination with statins to further reduce both LDL-C and ASCVD risk.
- PCSK9 inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with familial hypercholesterolemia.
- PCSK9 inhibitors should be considered in individuals with clinical CV disease who are unable to reach LDL-C/non-HDL-C goals with maximally-tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals.
- Combination therapy of lipid-lowering agents should be considered when the LDL-C/non-HDL-C levels are markedly increased and monotherapy (usually with a statin) does not achieve the therapeutic goal.
- The guidelines discuss the FOURIER trial with Repatha. There is a statement that additional ASCVD benefit in very high-risk individuals with further lowering of LDL-C to < 55 mg/dL using statin therapy in combination with ezetimibe (IMPROVE-IT trial) or a PCSK9 inhibitor forms the basis of the recommendation for a new category of risk, extreme risk, with an LDL-C goal < 55 mg/dL.

European Atherosclerosis Society (EAS)
A position paper from the EAS Consensus Panel on Familial Hypercholesterolaemia provides diagnostic criteria for homozygous familial hypercholesterolemia (HoFH). Diagnosis is made either genetically or clinically.

- Genetic confirmation of two mutant alleles at the LDLR, APOB, PCSK9, or LDLRAP1 gene locus OR
- An untreated LDL-C >13 mmol/L (500 mg/dL) or treated LDL-C ≥ 8 mmol/L (300 mg/dL)* together with either:
  - Cutaneous or tendon xanthoma before age 10 years or
  - Untreated elevated LDL-C levels consistent with heterozygous FH in both parents

  ** These LDL-C levels are only indicative, and lower levels, especially in children or in treated patients, do not exclude HoFH*

The panel also provides a suggested algorithm for the management of HoFH and recommends LDL-C targets of less than 100 mg/dL (< 2.5 mmol/L) for adults; less than 135 mg/dL (< 3.5 mmol/L) for children; and less than 70 mg/dL (< 1.8 mmol/L) if clinical cardiovascular disease. Management strategies include a combination of statin therapy (at highest dose depending on tolerability) with or without ezetimibe and LDL-apheresis every 1 or 2 weeks. The panel also notes that lomitapide and mipomersen are available as adjunctive treatments. PCSK9 inhibitors are mentioned as future therapeutic options (Cuchel, 2014).

National Lipid Association (NLA)
In 2017, an expert panel from the NLA published recommendations on the use of PCSK9 inhibitors in adults. Guidance is given for three patient-specific populations (Orringer, 2017).
Patients with ASCVD:

- For patients with ASCVD, PCSK9 inhibitor therapy should be considered for ASCVD risk reduction in patients with stable ASCVD, particularly in those with additional ASCVD risk factors, on maximally-tolerated statin therapy with or without ezetimibe, with on-treatment LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL (Strength A, Quality: High).
- PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients with progressive ASCVD on maximally-tolerated statin therapy, with or without ezetimibe, and on-treatment LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL (Strength B, Quality: Moderate).

Patients with LDL-C ≥ 190 mg/dL (including polygenic hypercholesterolemia, HeFH and HoFH):

- PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients 40 to 79 years of age with pre-treatment LDL-C ≥ 190 mg/dL, no uncontrolled ASCVD risk factors, or other key additional high-risk markers,

and on-treatment LDL-C ≥ 100 mg/dL or non-HDL-C ≥ 130 mg/dL on maximally-tolerated statin therapy ± ezetimibe (Strength B, Quality: Moderate). High-risk markers include a history of uncontrolled high blood pressure, diabetes, current cigarette smoking, or family history of premature ASCVD; or additional high-risk markers (coronary calcium ≥ 300 Agatston units; Lipoprotein a ≥ 50 mg/dL using isoform insensitive assay, high-sensitivity C-reactive protein ≥ 2 mg/L or CKD including albumin/creatinine ratio ≥ 30 mg/g.

- PCSK9 inhibitor therapy may be considered for additional LDL-C reduction in patients 40 to 79 years of age with pre-treatment LDL-C ≥ 190 mg/dL, and the presence of either uncontrolled ASCVD risk factors, key additional high-risk markers, or genetic confirmation of familial hypercholesterolemia (FH), and on-treatment LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL on maximally-tolerated statin with or without ezetimibe (Strength B, Quality: Moderate).
- PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients 18 to 39 years of age with pre-treatment LDL-C ≥ 190 mg/dL, and the presence of either uncontrolled ASCVD risk factors, key additional risk-markers, or genetic confirmation of FH, and on-treatment LDL-C ≥ 100 mg/dL or non-HDL-C ≥ 130 mg/dL on maximally-tolerated statin, with or without ezetimibe (Strength E, Quality: Low).
- PCSK9 inhibitor therapy may be considered to further reduce LDL-C in patients with HoFH, either of unknown genotype, or those known to be LDL receptor defective, on maximally-tolerated statin therapy with or without ezetimibe with LDL-C ≥ 70 mg/dL or non-HDL-C ≥ 100 mg/dL (Strength B, Quality: Moderate).

Very High-Risk/Statin Intolerance:

- PCSK9 inhibitor therapy may be considered to further reduce LDL-C in selected very-high-risk patients who meet the definition of statin intolerance (as previously defined by the NLA Statin Expert Panel) and who require substantial additional atherogeneic cholesterol lowering, despite use of other lipid-lowering therapies (Strength C, Quality: Low).

The American Board of Internal Medicine's (ABIM) Foundation Choosing Wisely® Initiative

No recommendations are available for PCSK9 Inhibitors.

Centers for Medicare & Medicaid Services - National Coverage Determinations (NCDs)

There are no CMS National Coverage Determinations for PCSK9 Inhibitors.

Clinical Efficacy

- **Alirocumab (Praluent)**

The efficacy and safety of alirocumab demonstrated in 5 clinical trials was used to support its use in the treatment of primary hyperlipidemia in ASCVD and HeFH. ODYSSEY LONG TERM enrolled adults (n = 2,341) with HeFH (diagnosed either through genotyping or clinical criteria [definite FH with Simon Broome or WHO/Dutch Lipid Network criteria]) or with established coronary heart disease (CHD) or a CHD risk equivalent with an LDL-C of 70 mg/dL or greater. All subjects were receiving either high-dose statin or maximally tolerated statin (with or without other lipid lowering therapy) and were randomized to alirocumab 150 mg every 2 weeks or placebo. Alirocumab-treated patients had a 61% reduction in LDL-C from baseline to week 24 (Robinson, 2015). ODYSSEY-COMBO I enrolled adults with either an LDL-C 70 mg/dL or greater and established cardiovascular disease or an LDL-C 100 mg/dL or greater and CHD risk equivalents. A total of 316 patients were enrolled and randomized to either alirocumab 75 mg every 2 weeks (with titration to 150 mg every 2 weeks based on LDL-C levels) or placebo. All patients were continued on maximally tolerated statin therapy with or without other lipid lowering therapy. Alirocumab produced a 48% reduction in LDL-C from baseline to week 24 (Kereiakes, 2015).

The other 3 clinical trials (ODYSSEY FH I, FH II, and HIGH FH) used to support FDA approval of alirocumab enrolled individuals with HeFH (diagnosed by genotyping or clinical criteria) on maximally tolerated statin with or without other lipid lowering therapy. ODYSSEY FH I and II randomized patients to either alirocumab 75 mg every 2 weeks (with titration to 150 mg every 2 weeks based on LDL-C levels) or placebo. Alirocumab produced a 57.9% reduction in LDL-C in FH I and a 51.4% reduction in FH II from baseline to week 24 and maintained these reductions to week 78 (Kastelein, 2015). ODYSSEY HIGH-FH is unpublished and enrolled individuals with a baseline LDL-C of at least 160 mg/dL and randomized to either alirocumab 150 mg every 2 weeks or placebo. The mean percent change from baseline to week 24 in LDL-C was -43% with alirocumab (Sanofi-Aventis U.S. LLC, 2015).

Cardiovascular Outcomes Data - alirocumab (Praluent)

ODYSSEY Outcomes was the CV outcomes trial involving Praluent, when added onto high-intensity statins with or without or other LMTs (lipid modifiying therapy), in patients who had recently experienced an acute coronary syndrome (ACS).The trial was a Phase III, multicenter, international, randomized, double-blind, placebo-controlled study (n = 18,924) that evaluated the effect of Praluent (75 or 150 mg SC Q2W) among patients who had experienced a recent ACS event. Patients were followed for up to 5 years. At Month 2, if additional LDL-C lowering was needed based on prespecified LDL-C criteria (LDL-C ≥ 50 mg/dL), the Praluent dose was adjusted to 150 mg SC Q2W. The target range for LDL-C was 25 to 50 mg/mL. Patients were ≥ 40 years of age and had experienced an ACS event (acute MI or unstable angina) within 1 to 12 months prior to randomization. Those involved in the trial had inadequate control of lipids (e.g., LDL-C ≥ 70 mg/mL, non high-density lipoprotein cholesterol [non-HDL-C] ≥ 100 mg/dL) despite receipt of high-intensity statins (atorvastatin 40 mg or 80 mg daily or rosuvastatin 20 or 40 mg daily). Some exclusion criteria included uncontrolled hypertension, New York Heart Association class III or IV heart failure, and a history of hemorrhagic stroke. The primary endpoint was the time to the first occurrence of one of the following: CHD death, non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina that required hospitalization. Other secondary endpoints were also evaluated (CV death, all-cause death, major CHD event) (Schwartz, 2018).

Results. The follow-up was a median of 2.8 years. Premature discontinuation occurred in 15% of patients, which occurred at similar rates among the groups. Per study protocol, around 8% of patients had a blinded switch from Praluent to placebo due to two consecutive LDL-C values < 15 mg/mL while receiving Praluent 75 mg SC Q2W. Around 27% of patients given Praluent (n = 2,615/9,451) required dose adjustment to 150 mg SC Q2W. Of these 2,615 patients, around 31% of patients (n = 805/2,615) were down titrated to 75 mg SC Q2W. At 4 months post-randomization, the mean LDL-C levels were 40 mg/dL and 93 mg/dL for Praluent and placebo, respectively, representing an approximate -63% decrease in LDL-C levels with adding Praluent. At 48 months post-randomization, LDL-levels were 66 mg/dL and 103 mg/dL respectively, for patients randomized to Praluent and placebo, representing an approximately -55% decrease in LDL-C levels (Schwartz, 2018).

- **Evolocumab (Repatha)**

The safety and efficacy of evolocumab supporting its FDA approval was established in 4 pivotal trials. LAPLACE-2 included individuals with primary hypercholesterolemia and mixed dyslipidemia who had a specified LDL-C level based on the presence and intensity of statin therapy. A total of 1,899 patients were enrolled and the FDA evaluated a subset of 296 patients with ASCVD. Evolocumab 420 mg once monthly or 140 mg every 2 weeks were compared to placebo and all patients were stabilized on a baseline statin regimen. The primary endpoint evaluated percent change from baseline LDL-C to week 12 and was -58% for the monthly regimen and -67% for the every 2 week evolocumab regimen (Amgen, 2015; Robinson, 2014). DESCARTES enrolled adults with a baseline LDL-C of at least 75 mg/dL. Approximately 900 patients were enrolled and the FDA evaluated 139 patients with ASCVD. Evolocumab 420 mg once monthly was compared to placebo as add-on therapy to background lipid-lowering treatment. Evolocumab decreased LDL-C from baseline to week 52 by 52% (Amgen, 2015; Blom, 2014).

RUTHERFORD-2 enrolled adults who met the Simon-Broome clinical criteria for heterozygous familial hypercholesterolemia (HeFH) who were on stable lipid lowering therapy. A total of 329 patients were randomized to evolocumab 420 mg monthly, evolocumab 140 mg every 2 weeks, or placebo. At week 12 LDL-C reduced by 61% in the evolocumab every 2 weeks group and 56% in the evolocumab monthly group (Raal, 2015b). TESLA-B included patients 12 years of age and older (13 years of age and older enrolled) with homozygous FH (HoFH) diagnosed either genetically or clinically. Exclusion criteria included use of mipomersen or lomitapide within the previous 5 months and lipoprotein apheresis within 8 weeks. All patients in the trial were on statin therapy and 92% were on ezetimibe. Evolocumab 420 mg once monthly lowered LDL-C 23% from baseline to week 12 (Raal, 2015a).

Cardiovascular (CV) Outcomes Data - Evolocumab (Repatha)

The FOURIER (Further cardiovascular OUtcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) trial with Repatha was a randomized, double-blind, placebo-controlled, multinational, event-driven, CV outcomes trial involving 27,564 patients with ASCVD with LDL-C levels ≥ 70 mg/dL who were receiving high or moderate intensity statin therapy. Patients were randomized to receive Repatha SC (either 140 mg Q2W or 420 mg QM) or placebo, in addition to background statin therapy (± ezetimibe). Patients were between 40 and 85

years of age and had clinically evident ASCVD, defined as a history of MI, nonhemorrhagic stroke, or symptomatic PAD, as well as additional attributes that classified the patients at higher CV risk. Patients had to be receiving an optimized regimen of lipid-lowering therapy, which was preferably a high-intensity statin but must have been at least atorvastatin ≥ 20 mg QD or its equivalent, with or without ezetimibe. The primary efficacy endpoint was major CV events defined as the composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. A key secondary efficacy endpoint was the composite of CV death, MI, or stroke (Sabatine, 2017).

Results. The 140 mg SC Q2W regimen was used by 86% of patients in the study. After 48 weeks of therapy, Repatha, in addition to background statin therapy, reduced LDL-C levels by 59% from a median baseline value of 92 mg/dL to 30 mg/dL. The median duration of follow-up was 26 months. The primary endpoint occurred in 9.8% of patients randomized to Repatha plus background statin therapy compared with 11.3% of patients in the placebo group which received background statin therapy only (HR, 0.85; 95% CI: 0.79, 0.92; P < 0.001). The key secondary endpoint was also significantly reduced for patients given Repatha plus background statin therapy (5.9% [n = 816]) compared with placebo plus background statin therapy (7.4% [n = 1,013]) [HR 0.80; 95% CI: 0.73, 0.88; P < 0.001). The endpoint of MI occurred among 3.4% of patients given Repatha plus statins compared with 4.6% of patients who received placebo plus statins (P < 0.001). Death from any cause did not differ between the two groups (3.2% vs. 3.1%; P = 0.54). The incidence of CV death also did not differ among the groups (1.8% vs. 1.7%; P = 0.62) (Sabatine, 2017).

Off Label Uses

AHFS Drug Information 2019 Edition does not support any off-label uses of alirocumab (Praluent) or evolocumab (Repatha).

Experimental, Investigational, Unproven Uses

- PCSK9 inhibitors work by preventing PCSK9 from binding to the LDLR receptor, which leads to receptor breakdown. With PCSK9 inhibition, the LDLR receptor can be recycled to the liver for further use to decrease LDL levels. This requires a functional LDL receptor to be effective. Therefore, homozygous or compound heterozygous LDLR genetics null mutations are not recommended for PCSK9 therapy as the medication is not effective without a functional LDLR gene (Baum, 2017).

- At this time, there is insufficient evidence to support the use of PCSK9 inhibitors for the prevention of cardiovascular events in patients without established cardiovascular disease.

- Concurrent use of evolocumab (Repatha) with alirocumab (Praluent) or lomitapide (Juxtapid). Praluent is another PCSK9 inhibitor and should not be used with Repatha (Roth, 2016). Juxtapid, a microsomal triglyceride transfer protein inhibitor, is indicated as an adjunct to lipid-lowering medications and diet to modify lipid parameters (e.g., reduce LDL-C levels) in patients with HoFH (Stroes, 2016). The efficacy and safety of using Praluent or Juxtapid in combination with Repatha have not been established.

APPENDIX 1 – WHO Criteria (Dutch Lipid Network Clinical Criteria) for Diagnosis of Heterozygous Familial Hypercholesterolemia (HeFH) (Nordestgaard, 2013)

Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia	
Family History	
First degree relative with known premature (men < 55 yrs, women < 60 yrs) coronary vascular disease	1
First degree relative with known LDL-cholesterol >95th percentile for age and sex	
and/or	
First degree relative with tendon xanthomata and/or arcus cornealis	2
Children below 18 yrs with LDL-cholesterol >95th percentile for age and sex	

Clinical History			
Patient has premature (men < 55 yrs, women < 60 yrs) coronary artery disease			2
Patient has premature (men < 55 yrs, women < 60 yrs) cerebral or peripheral vascular disease			1
Physical Examination			
Tendon xanthomata			6
Arcus cornealis below the age of 45 yrs			4
Laboratory Analysis			
	mmol/L	mg/dL	
LDL-cholesterol	> 8.5	> 330	8
LDL-cholesterol	6.5 – 8.4	250 – 329	5
LDL-cholesterol	5.0 – 6.4	190 – 249	3
LDL-cholesterol	4.0 – 4.9	155 – 189	1
(HDL-cholesterol and triglycerides are normal)			
DNA Analysis			
Functional mutation low-density lipoprotein receptor gene present			6
Diagnosis of HeFH is:			
Certain When		> 8 points	
Probable When		6-8 points	
Possible When		3-5 points	

APPENDIX 2 – Simon Broome Register Diagnostic Criteria for Heterozygous Familial Hypercholesterolemia (HeFH) (Scientific Steering Committee, 1991)

Definite familial hypercholesterolemia is defined as:

- Total cholesterol > 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years or total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment)

PLUS

- Tendon xanthomas in patient or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt)

OR

- DNA-based evidence of an LDL receptor mutation or familial defective apo B-100

Possible familial hypercholesterolemia is defined as:

- Total cholesterol > 6.7 mmol/L (260 mg/dl) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years or total cholesterol > 7.5 mmol/L (290 mg/dl) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment)

And at least one of the following:

- Family history of myocardial infarction below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative.
- Family history of raised cholesterols > 7.5 mmol/L (290 mg/dL) in adult 1st or 2nd degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling under 16 years of age.

Coding/ Billing Information

Note: PCSK9 Inhibitors are typically covered under pharmacy benefit plans. Certain prescription drugs require an authorization for coverage to ensure that appropriate treatment regimens are followed. Medical drug coding

and diagnosis codes, however, are generally not required for pharmacy claims submissions, therefore, this section is not in use.

References

1. Amgen Inc. Repatha (evolocumab) injection, for subcutaneous use [product information]. Thousand Oaks, CA: Amgen Inc. December 2017. Accessed 10/3/2019.
2. Baum SJ, Toth PP, Underberg JA, Jellinger P, Ross J, Wilemon K. PCSK9 inhibitor access barriers-issues and recommendations: Improving the access process for patients, clinicians and payers. Clin Cardiol. 2017 Apr; 40(4):243-254.
3. Bays, HE, et al. National Lipid Association Annual Summary of Clinical Lipidology 2016. Journal of Clinical Lipidology (2016) 10, S1-S43.
4. Benner JS, Glynn RJ, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. JAMA 2002; 288: 455-61.
5. Blom DJ, Hala T, Bolognese M, Lillestol MJ, et al; DESCARTES Investigators. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med 2014; 370 (19): 1809-19.
6. Centers for Disease Control and Prevention (CDC). Vital signs: prevalence, treatment, and control of high levels of low-density lipoprotein cholesterol: United States, 1999–2002 and 2005–2008. MMWR Morb Mortal Wkly Rep. 2011; 60:109–114.
7. Cuchel M, Bruckert E, Ginsberg HN, et al for the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolaemia. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014; 35: 2146–57.
8. Gidding SS, Ann Champagne M, de Ferranti SD, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement from the American Heart Association. Circulation. 2015 Dec 1; 132 (22): 2167-92.
9. Grundy SM, Stone NJ, Bailey AL, et al ACC/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2018 Nov 10. [Epub ahead of print]. Available at: https://www.ahajournals.org/doi/pdf/10.1161/CIR.0000000000000625. Accessed on 10/4/19.
10. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association Recommendations for patient-centered management of dyslipidemia: Part 1 – Full Report. J Clin Lipidol 2015; Article in Press. Available from: https://www.lipid.org/sites/default/files/PIIS1933287415000598.pdf
11. Bays, H.E., Jones P.H., et al. National Lipid Association Annual Summary of Clinical Lipidology 2016. J Clin Lipidol. 2016; 10: S1–S43
12. Jellinger PS, Handelsman Y, et al. AACE 2017 Guidelines: For Management of Dyslipidemia and Prevention of Cardiovascular Disease. Endocrine Practice Vol 23 (Suppl 2) April 2017. Available at: https://www.aace.com/files/lipid-guidelines.pdf. Accessed on 10/4/2019.
13. Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolemia. Eur Heart J 2015; 36 (43): 2996-3003.
14. Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisn/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. Am Heart J 2015; 169 (6): 906-15.
15. Koren MJ, Lundqvist P, Bolognese M, et al; MENDEL-2 Investigators. Anti-PCSK9 monotherapy for hypercholesterolemia: the MENDEL-2 randomized, controlled phase III clinical trial of evolocumab. J Am Coll Cardiol 2014; 63 (23): 2531-40.
16. Landmesser, Ulf, et al. 2017 Update of ESC/EAS Task Force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. European Heart Journal (2017) 0, 1–13.
17. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the

Management of Atherosclerotic Cardiovascular Disease Risk. Journal of the American College of Cardiology; Volume 70, Issue 14, Pages 1785-1822.
18. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143–3421.
19. Nordestgaard BG, Chapman MJ, Humphries SE, et al for the European Atherosclerosis Society Consensus Panel. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: Consensus statement of the European Atherosclerosis Society. Eur Heart J 2013; 34 (45): 3478-90a.
20. Orringer, Carl E. et al. Update on the use of PCSK9 inhibitors in adults: Recommendations from 2017 Expert Panel of the National Lipid Association. Journal of Clinical Lipidology, Volume 11, Issue 4, 880 – 890. Available at: http://www.lipidjournal.com/article/S1933-2874(17)30290-8/pdf. Accessed on 10/4/19.
21. Raal FJ, Honarpour N, Blom DJ, et al; TESLA Investigators. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet 2015(a); 385 (9965): 341-50.
22. Raal FJ, Stein EA, Dufour R, et al; RUTHERFORD-2 Investigators. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolaemia (RUTHERFORD-2): a randomised, double-blind, placebo-controlled trial. Lancet 2015(b); 385 (9965): 331-40.
23. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 2015; 372 (16): 1489-99.
24. Robinson JG, Nedergaard BS, Rogers WJ, et al; LAPLACE-2 Investigators. Effect of evolocumab or ezetimibe added to moderate- or high intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA 2014; 311 (18): 1870-82.
25. Roth EM, Taskinen MR, Ginsberg HN, et al. Monotherapy with the PCSK9 inhibitor alirocumab versus ezetimibe in patients with hypercholesterolemia: results of a 24 week, double-blind, randomized Phase 3 trial. Int J Cardiol 2014; 176 (1): 55-61.
26. Roth EM, Moriarty PM, Bergeron J, et al, for the ODYSSEY CHOICE I Investigators. A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I. *Atherosclerosis*. 2016;254:254-262.
27. Sabatine MS, Giugliano RP, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017; 376:1713-1722.
28. Sanofi-Aventis U.S. LLC. Praluent (alirocumab) for injection, for subcutaneous use [product information]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC. September 2017. Accessed 10/3/19.
29. Scientific Steering Committee on behalf of the Simon Register Group. Risk of fatal coronary heart disease in familial hypercholesterolaemia. BMJ 1991; 303: 893–6.
30. Schwartz GG, Steg PG, Azarek M, et al, for the ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med*. 2018;379:2097-2107.
31. Stroes E, Guyton JR, Lepor N, et al, for the ODYSSEY CHOICE II Investigators. Efficacy and safety of alirocumab 150 mg every 4 weeks in patients with hypercholesterolemia not on statin therapy: the ODYSSEY CHOICE II Study. *J Am Heart Assoc*. 2016;5(9):e003421.