



PRIOR AUTHORIZATION POLICY

POLICY: Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors – Repatha® (evolocumab injection for subcutaneous use [single-use prefilled syringes and Pushtronex™ system] – Amgen)

TAC APPROVAL DATE: 06/12/2019

OVERVIEW

Repatha, a proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor antibody, is indicated: 1) to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization in adults with established cardiovascular (CV) disease; 2) as an adjunct to diet, alone and in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) to reduce low-density lipoprotein cholesterol (LDL-C); and 3) as an adjunct to diet and other low-density lipoprotein (LDL) therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.¹ The safety and effectiveness of Repatha have not been established in pediatric patients with primary hyperlipidemia or HeFH. The safety and effectiveness of Repatha have not been established in pediatric patients with HoFH aged < 13 years.

Clinical Efficacy

The efficacy of Repatha was assessed in several studies which mainly involved patients at high risk (e.g., background atherosclerotic cardiovascular disease, HeFH) who received Repatha along with maximally tolerated doses of statins, with or without other lipid-modifying therapies. The LDL-C reductions when Praluent was added onto statin therapy ranged from approximately 50% to 60% at the time of the efficacy endpoint evaluations (e.g., 12 or 24 weeks).¹ Longer-term follow-up, including extension studies, are also available.

Cardiovascular (CV) Outcomes Data

The FOURIER (Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk) trial with Repatha was a randomized, double-blind, placebo-controlled event-driven trial involving over 27,000 patients with ASCVD with LDL-C levels ≥ 70 mg/dL.^{1,2} Patients were between 40 and 85 years of age and had clinically evident ASCVD, defined as a history of MI, nonhemorrhagic stroke, or symptomatic peripheral arterial disease (PAD), as well as additional attributes that classified the patients at higher CV risk.^{1,2} Patients were randomized to receive Repatha SC (either 140 mg Q2W or 420 mg QM) or placebo, in addition to background statin therapy (\pm ezetimibe). The primary efficacy endpoint was the composite of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. The average patient age was 62 years.^{1,2} 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.² The median duration of follow-up was 26 months. The primary endpoint occurred in 9.8% of patients (n = 1,344) randomized to Repatha plus background statin therapy compared with 11.3% of patients in the placebo group (n = 1,563) which received background statin therapy only, representing a statistically significant 15% reduction. The findings of this study suggest that lowering LDL-C levels with Repatha, in addition to continuing to receive background statin therapy, reduces the risk of adverse CV events among patients with background ASCVD. Death from any cause did not differ between the two groups (3.2% vs. 3.1%; P = 0.54).

Guidelines

Many guidelines are available regarding the treatment of patients with dyslipidemia.³⁻¹⁰ For patients with elevated LDL-C, statins are the cornerstone of therapy and recommended first-line to be used at maximally tolerated doses due to the established benefits regarding the reduction of CV risks. Atorvastatin 40 mg to 80 mg QD and rosuvastatin 20 mg to 40 mg QD are considered high-intensity statins as they achieve LDL-C lowering of $\geq 50\%$. Other statin regimens, including atorvastatin and rosuvastatin at lower doses are classified as moderate-intensity (LDL-C reductions of 30% to 49%) products and low-intensity agents (LDL-C reductions $< 30\%$). The American Heart Association (AHA)/American College of Cardiology (ACC) guidelines on the management of blood cholesterol (2018) defines ASCVD as ACS, those with a history of MI, stable or unstable angina or coronary or other revascularizations, stroke, TIA, or PAD.¹⁰ Although LDL-C thresholds are not always recognized, in general, an LDL-C < 70 mg/dL is recommended in for most patients with ASCVD to reduce CV risk. Use of a PCSK9 as an adjunct is justified if this goal is not met with maximally tolerated statins.¹⁰ Additionally, guidelines and reviews have recognized that patients with a CAC score ≥ 300 Agatston units are at an increased risk of CV events.¹⁰⁻¹³

In 2011, the NLA published guidelines for the screening, diagnosis, and management of pediatric and adult patients with FH.¹⁴ FH encompasses a group of genetic defects that cause severe elevations in LDL-C levels, as well as other lipid parameters. HeFH occurs in approximately 1 in 300 to 500 patients and is present in childhood. Total cholesterol (total-C) levels in HeFH range from 350 to 550 mg/dL, which can result in premature ASCVD. Aggressive lipid-lowering therapy is recommended to achieve LDL-C reductions of at least 50%. Both children and adults with LDL-C levels ≥ 190 mg/dL following lifestyle modifications will require medication therapy. Statins are the initial treatment for all adults with FH. High or moderate intensity statins are recommended; low potency statins are generally inadequate for patients with FH due to the markedly elevated LDL-C levels. In the pivotal trials for Praluent, HeFH was diagnosed utilizing Simon Broome criteria or Dutch Lipid Clinical Network criteria.¹ In an AHA scientific statement, it describes the Dutch Lipid Clinical Network Criteria and states that a score of > 5 on the scale makes the diagnosis of FH highly probable.¹⁵ Also, genetic testing can reveal a diagnosis of HeFH and clinical manifestations (e.g., tendon xanthomata) are highly suggestive of the condition.²³⁻²⁴ Also, patients with an untreated LDL-C ≥ 190 mg/dL suggest FH.¹⁵⁻¹⁷ In general, for patients with HeFH who have not yet manifested ASCVD, LDL-C levels ≤ 100 mg/dL are recommended. The addition of a PCSK9 inhibitor to statin therapy can be considered if this goal is not achieved.

In 2019 the AHA issued a scientific statement regarding statin safety and associated adverse events.¹⁸ In general, statins are well-tolerated agents that have successfully led to decreased LDL-C levels which led to reductions in CV events (e.g., MI, ischemic stroke). The risk of serious statin-induced muscle injury (e.g., rhabdomyolysis) is low ($< 0.01\%$). In US clinical practice, about 10% of patients stop taking statin therapy due to subjective complaints, of which muscle symptoms without significantly raised CK levels are noted. Data suggests that the muscle symptoms that occur among patients are not caused by the pharmacologic effects of the statin and restarting statin therapy for these patients is important, especially among patients at high risk of CV events, for whom CV event prevention is important. Several studies have shown that patients were believing that they were “statin intolerant”. However, many patients were able to subsequently tolerate a statin upon rechallenge and receive the benefits provided with these agents. Other data supports this occurrence.^{19,20}

HoFH is a rare inherited condition in which LDL-C is not adequately removed from the body, resulting in high levels of circulating LDL-C.^{14,17} The 2014 HoFH position paper from the Consensus Panel on FH of the European Atherosclerosis Society states the diagnosis of HoFH is made based on genetic or clinical criteria.¹⁷ A definitive diagnosis can be made by genetic confirmation of two mutant alleles at the LDLR,

APOB, PCSK9, or LDLRAP1 gene locus. However, in some patients genetic confirmation remains elusive. Historically, HoFH has been commonly diagnosed based on LDL-C levels such as an untreated LDL-C > 500 mg/dL, or a treated LDL-C \geq 300 mg/dL. Also confirming the diagnosis is the presence of xanthomas (cutaneous or tendinous) before the age of 10 years or a family history of elevated LDL-C levels consistent with HeFH in both parents.¹⁷ Other clinical manifestations of HoFH include arcus cornea or xanthelasma.^{14,17}

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Repatha. Due to the specialized skills required for evaluation and monitoring of this new therapy, approval requires Repatha to be prescribed by or in consultation with a physician who specializes in the condition being treated. All approvals are provided for 3 years in duration.

Documentation: None required.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Repatha is recommended in those who meet the following criteria:

FDA-Approved Indications

- 1. Atherosclerotic Cardiovascular Disease (ASCVD) [Clinical].*** Approve Repatha for 3 years if the patient meets the following criteria (A, B, C, and D):
 - A)** The patient is aged \geq 18 years; **AND**
 - B)** The patient has had one of the following conditions or diagnoses (i, ii, iii, iv or v):
 - i.** The patient has had a previous myocardial infarction (MI) or has a history of an acute coronary syndrome (ACS); **OR**
 - ii.** The patient has a diagnosis of angina (stable or unstable); **OR**
 - iii.** The patient has a past history of stroke or transient ischemic attack (TIA); **OR**
 - iv.** The patient has peripheral arterial disease (PAD); **OR**
 - v.** The patient has undergone a coronary or other arterial revascularization procedure in the past (e.g., coronary artery bypass graft [CABG], percutaneous coronary intervention [PCI], angioplasty, coronary stent procedure); **AND**
 - C)** The patient meets one of the following criteria (i or ii):
 - i.** The patient has tried one high-intensity statin therapy (i.e., atorvastatin \geq 40 mg daily; rosuvastatin tablets \geq 20 mg daily [as a single-entity or as a combination product]) for \geq 8 continuous weeks **AND** the LDL-C level after this treatment regimen remains \geq 70 mg/dL; **OR**
 - ii.** The patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
 - a)** The patient experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually associated with markedly elevated creatine kinase [CK] levels [at least 10 times the upper limit of normal], along with evidence of end organ damage which can include signs of acute renal injury [noted by substantial increases in serum creatinine {Scr} levels {a \geq 0.5 mg/dL increase in Scr or doubling of the Scr}] and/or myoglobinuria [myoglobin present in urine]); **OR**

- b) The patient experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:
 - (1) The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
 - (2) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
 - D) Repatha is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.
- 2. Heterozygous Familial Hypercholesterolemia (HeFH).*** Approve Repatha for 3 years if the patient meets the following criteria (A, B, C, and D):
- A) The patient is aged ≥ 18 years; AND
 - B) The patient meets one of the following criteria (i, ii, iii, iv or v):
 - i. The patient has an untreated LDL-C ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); OR
 - ii. The patient has genetic confirmation of HeFH by mutations in the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene; OR
 - iii. The patient has been diagnosed with HeFH meeting one of the following diagnostic criteria thresholds (a or b):
 - a) The prescriber used the Dutch Lipid Network criteria and the patient has a score > 5 ; OR
 - b) The prescriber used the Simon Broome criteria and the patient met the threshold for “definite” or “possible” familial hypercholesterolemia; OR
 - iv. The patient has clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma); OR
 - v. The patient has a treated low-density lipoprotein cholesterol (LDL-C) level ≥ 100 mg/dL (after treatment with antihyperlipidemic agents but prior to PCSK9 inhibitor therapy such as Praluent® [alirocumab injection for SC use] or Repatha); AND
 - C) The patient meets one of the following criteria (i or ii):
 - i. The patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin tablets ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks AND the LDL-C level after this treatment regimen remains ≥ 70 mg/dL; OR
 - ii. The patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
 - a) The patient experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually associated with markedly elevated creatine kinase [CK] levels [at least 10 times the upper limit of normal], along with evidence of end organ damage which can include signs of acute renal injury [noted by substantial increases in serum creatinine {Scr} levels {a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr}] and/or myoglobinuria [myoglobin present in urine]); OR

- b) The patient experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:
 - (1) The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
 - (2) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
 - D) Repatha is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.
- 3. Homozygous Familial Hypercholesterolemia (HoFH).*** Approve Repatha for 3 years if the patient meets the following criteria (A, B, C, and D):
- A) The patient is aged ≥ 13 years; AND
 - B) The patient meets one of the following (i, ii, iii or iv):
 - i. The patient has genetic confirmation of two mutant alleles at the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), proprotein convertase subtilisin kexin type 9 (PCSK9) or low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene locus; OR
 - ii. The patient has an untreated low-density lipoprotein (LDL-C) level > 500 mg/dL (prior to treatment with antihyperlipidemic agents); OR
 - iii. The patient has a treated low-density lipoprotein cholesterol (LDL-C) level ≥ 300 mg/dL (after treatment with antihyperlipidemic agents but prior to agents such as Repatha or Juxtapid[®] [lomitapide capsules]); OR
 - iv. The patient has clinical manifestations of HoFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma); AND
 - C) The patient meets one of the following criteria (i or ii):
 - i. The patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks AND the low-density lipoprotein cholesterol (LDL-C) level after this treatment regimen remains ≥ 70 mg/dL; OR
 - ii. The patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
 - a) The patient experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually associated with markedly elevated creatine kinase [CK] levels [at least 10 times the upper limit of normal], along with evidence of end organ damage which can include signs of acute renal injury [noted by substantial increases in serum creatinine {Scr} levels {a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr}] and/or myoglobinuria [myoglobin present in urine]); OR
 - b) The patient experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:
 - (1) The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND

- (2) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
- D) Repatha is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.
4. **Primary Hyperlipidemia (not associated with ASCVD, HeFH, or HoFH).*** [Note: This may be referred to as combined hyperlipidemia, hypercholesterolemia {pure, primary}, dyslipidemia, increased/elevated LDL-C]. Approve Repatha for 3 years if the patient meets the following criteria (A, B, C, and D):
- A) The patient is aged ≥ 18 years; AND
- B) The patient has a coronary artery calcium or calcification (CAC) score ≥ 300 Agatston units; AND
- C) The patient meets one of the following criteria (i or ii):
- i. The patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin tablets ≥ 20 mg daily [as a single-entity or as a combination product]) AND ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; AND the LDL-C level after this treatment regimen remains ≥ 100 mg/dL; OR
- ii. The patient has been determined to be statin intolerant by meeting one of the following criteria (a or b):
- a) The patient experienced statin-related rhabdomyolysis (Note: Statin-induced muscle breakdown that is usually associated with markedly elevated creatine kinase [CK] levels [at least 10 times the upper limit of normal], along with evidence of end organ damage which can include signs of acute renal injury [noted by substantial increases in serum creatinine {Scr} levels {a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr}] and/or myoglobinuria [myoglobin present in urine]); OR
- b) The patient experienced skeletal-related muscle symptoms (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness]) and meets both of the following criteria [(1) and (2)]:
- (1) The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); AND
- (2) When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy, myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); AND
- D) Repatha is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

Note:

* Patients may have a diagnoses that pertain to more than one FDA-approved indication, therefore, consider review under different approval conditions, if applicable (e.g., patients with HeFH have had a clinical ASCVD event, patients with primary hyperlipidemia may have HeFH).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Repatha has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. Rationale for non-coverage for these specific conditions is provided below. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

1. **Concurrent use of Repatha with Praluent® (alirocumab injection for SC use) or Juxtapid (lomitapide capsules).** Praluent is another PCSK9 inhibitor and should not be used with Repatha.²¹ 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.²² The efficacy and safety of using Praluent or Juxtapid in combination with Repatha have not been established.
2. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Repatha® injection for subcutaneous use [prescribing information]. Thousand Oaks, CA: Amgen; February 2019.
2. Sabatine MS, Giugliano RP, Keech AC, et al, for the FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med.* 2017;376(18):1713-1722.
3. Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. *Circulation.* 2014;129(25 Suppl 2):S1-S45. Available at <http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a>. Accessed on June 1, 2019.
4. Lloyd-Jones DM, Morris, PB, Ballantyne CM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statins for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. *J Am Coll Cardiol.* 2016;68(1):92-125. Available at: https://ac.els-cdn.com/S0735109716323981/1-s2.0-S0735109716323981-main.pdf?_tid=f58ef706-e4f0-11e7-b6e6-00000aab0f26&acdnat=1513711102_24755cd3a7d35d3940446c644e07d8f8. Accessed on June 1, 2019.
5. 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-Statins Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease. *J Am Coll.* 2017;70(14):1785-1822. Available at: https://ac.els-cdn.com/S0735109717388988/1-s2.0-S0735109717388988-main.pdf?_tid=a9926172-18de-11e8-989d-00000aacb35d&acdnat=1519420712_18736a727a20c3fe386543af71cc5975. Accessed on June 1, 2019.
6. Jacobson TA, Ito MK, Maki KC, et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1-executive summary. *J Clin Lipidol.* 2014;8:473-488. Available at: [http://www.lipidjournal.com/article/S1933-2874\(14\)00274-8/pdf](http://www.lipidjournal.com/article/S1933-2874(14)00274-8/pdf). Accessed on June 1, 2019.
7. 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;9:129-169. Available at: [http://www.lipidjournal.com/article/S1933-2874\(15\)00059-8/pdf](http://www.lipidjournal.com/article/S1933-2874(15)00059-8/pdf). Accessed on June 1, 2019.
8. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients. *J Clin Lipidol.* 2011;5:S1-S8.
9. Orringer CE, Jacobson TA, Saseen JJ, et al. Update on the use of PCSK9 inhibitors in adults: recommendations from an Expert Panel of the National Lipid Association. *J Clin Lipid.* 2017;11:880-890. Available at: [http://www.lipidjournal.com/article/S1933-2874\(17\)30290-8/pdf](http://www.lipidjournal.com/article/S1933-2874(17)30290-8/pdf). Accessed on June 1, 2019.
10. 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 June 1, 2019.
11. Hect HS, Cronin P, Blaha M, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: A report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. *J Thorac Imaging.* 2017;32(5):W54-S66.
12. Blaha MJ, Mortensen MB, Kianoush S, et al. Coronary artery calcium scoring. Is it time for a change in methodology. *J Am Coll Cardiol Imag.* 2017;10:923-937.

13. Burge MR, Eaton RP, Comerci G, et al. Management of asymptomatic patients with positive coronary artery calcium scans. *J Endocr Soc.* 2017;1(6):588-599.
14. Goldberg AC, Hopkins PN, Toth PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients. *J Clin Lipidol.* 2011;5:S1-S8.
15. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. *Curr Opin Lipidol.* 2012;23:282-289.
16. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia. A scientific statement from the American Heart Association. *Circulation.* 2015;132(22):2167-2192.
17. Cuchel M, Bruckert E, Ginsberg HN, et al, for the European Atherosclerosis Society Consensus Panel on Familial Hypercholesterolemia. 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;35:2146-2157.
18. Newman VB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events. A scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol.* 2019;39:e38-e81.
19. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings. *Ann Intern Med.* 2013;158(7):526-534.
20. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic Experience. *Am Heart J.* 2013;166(3):597-603.
21. Praluent® injection for subcutaneous use [prescribing information]. Bridgewater, NJ and Tarrytown, NY: sanofi-aventis and Regeneron Pharmaceuticals; April 2019.
22. Juxtapid® capsules [prescribing information]. Cambridge, MA: Aegerion Pharmaceuticals; August 2017.

HISTORY

Type of Revision	Summary of Changes*	TAC Approval Date
Selected revision	Added additional diagnostic criteria defining HeFH as follows: LDL-C \geq 190 mg/dL (prior to treatment with antihyperlipidemic agents); the patient has genetic confirmation of HeFH; the patient has been diagnosed with HeFH meeting one of the following criteria thresholds of Dutch Lipid Network criteria score $>$ 5 or Simon Broome criteria with “definite” or “possible” FH; or the patient has clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma).	01/25/2017
Selected revision.	Approval duration changed for all indications from 12 months to 3 years. Also, data from the FOURIER CV outcomes trial with Repatha was added to the body of the document.	04/12/2017
Annual revision	For the criteria regarding clinical ASCVD, clarified that patients that only report having carotid artery stenosis and/or an elevated calcium score do not meet the requirements for clinical ASCVD.	09/13/2017
Selected revision	For the criteria regarding hyperlipidemia in clinical ASCVD and for patients with HeFH, removed the criteria that required the use of Zetia® (ezetimibe tablets, generic) [as a single-entity or as a combination product] for \geq 8 continuous weeks.	09/20/2017
Early annual revision	For the diagnosis regarding clinical ASCVD, the criteria that the patient have an LDL-C level \geq 70 mg/dL (after treatment with antihyperlipidemia agents but prior to PCSK9 inhibitor therapy) was removed. New criteria were added to address the new FDA-approved indication regarding primary hyperlipidemia. In summary, patients are required to be \geq 18 years of age; have a coronary artery calcium or calcification score \geq 300 Agatston units; have tried one high-intensity statin therapy and ezetimibe in combination for \geq 8 weeks AND the LDL-C after this treatment regimens remains \geq 100 mg/mL; and that the Repatha be prescribed by a specialist. There are also criteria to address statin intolerance.	2/21/2018
Early annual revision	Added that documentation is required for specific criteria on initial approval for all indications (ASCVD, HeFH, HoFH, and primary hyperlipidemia) [effective 7/1/2018]	05/02/2018
Early annual revision	For the criteria that addresses the diagnosis of HeFH among patients who have received treatment with antihyperlipidemic agents but prior to PCSK9 inhibitor therapy (such as Praluent and Repatha), changed the LDL-C level from \geq 160 mg/dL to \geq 100 mg/dL [effective 7/1/2018].	05/09/2018
Early annual revision	Documentation removed from the Policy that was set to be effective on 7/1/2018.	05/16/2018
Annual revision	Conditions Not Recommended for Approval: Kynamro was removed from the list of agents in which Repatha should not be used with concomitantly because this product is no longer available.	06/12/2019

* For a further summary of criteria changes, refer to respective TAC minutes available at: <http://esidepartments/sites/Dep043/Committees/TAC/Forms/AllItems.aspx>; TAC – Therapeutic Assessment Committee; HoFH – Homozygous familial hypercholesterolemia; DEU – Drug Evaluation Unit; PCSK9 – Proprotein convertase subtilisin kexin type 9; PA – Prior authorization; LDL-C – Low-density lipoprotein cholesterol, HeFH – Heterozygous familial hypercholesterolemia; FH – Familial hypercholesterolemia; CV – Cardiovascular; ASCVD – Atherosclerotic cardiovascular disease.

APPENDIX A.
Simon Broome Register Diagnostic Criteria¹⁵

Definite Familial Hypercholesterolemia:

- a) Raised cholesterol
 - (i) Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years;
 - (ii) Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult (aged > 16 years);
- b) AND
 - (i) Tendon xanthomas in the patient or in a first (parent, sibling, or child) or second-degree relative (grandparent, aunt, or uncle);
- c) OR
 - (i) DNA-based evidence of LDL-receptor, familial defective apo B-100, or PCSK9 mutation.

Possible Familial Hypercholesterolemia:

- a) Raised cholesterol
 - (i) Total cholesterol greater than 6.7 mmol/L (260 mg/dL) or LDL-C > 4.0 mmol/L (155 mg/dL) in a child < 16 years;
 - (ii) Total cholesterol > 7.5 mmol/L (290 mg/dL) or LDL-C > 4.9 mmol/L (190 mg/dL) in an adult;
- b) AND at least one of the following:
 - (i) Family history of premature myocardial infarction younger than 50 years of age in second-degree relative or younger than 60 years of age in first-degree relative;
- c) OR
 - (i) Family history of raised cholesterol > 7.5 mmol (290 mg/dL) in adult first-degree or second-degree relative or > 6.7 mmol/L (260 mg/dL) in child or sibling aged < 16 years.

APPENDIX B.
Dutch Lipid Network Criteria for Familial Hypercholesterolemia¹⁶

Criteria	Score
Family History	
First-degree relative with known premature coronary and/or vascular disease (men < 55 years, women < 60 years)	1
First degree relative with known LDL-C > 95 th percentile for age and sex	1
First-degree relative with tendon xanthomata and/or arcus cornealis, OR	2
Children aged < 18 years with LDL-C > 95 th percentile for age and sex	2
Clinical History	
Patient with premature CAD (age as above)	2
Patient with premature cerebral or peripheral vascular disease (age as above)	1
Physical Examination	
Tendon xanthomas	6
Arcus cornealis at age < 45 years	4
LDL-C	
LDL-C ≥ 8.5 mmol/L (330 mg/dL)	8
LDL-C 6.5 to 8.4 mmol/L (250 to 329 mg/dL)	5
LDL-C 5.0 to 6.4 mmol/L (190 to 249 mg/dL)	3
LDL-C 4.0 to 4.9 mg/dL (155 to 189 mg/dL)	1
DNA analysis	
Functional mutation LDLR, APOB or PCSK9 gene	8
Stratification	
Definite familial hypercholesterolemia	> 8
Probable familial hypercholesterolemia	6 to 8
Possible familial hypercholesterolemia	3 to 5
Unlikely familial hypercholesterolemia	< 3

LDL-C – Low-density lipoprotein cholesterol; CAD – Coronary artery disease; LDLR – Low-density lipoprotein receptor; APOB – Apolipoprotein B; PCSK9 – Proprotein convertase subtilisin kexin type 9.