Washington State Health Care Authority

Antihyperlipidemics –
Proprotein Convertase Subtilisin Kexin Type 9 (PCSK-9) Inhibitors

Medical policy no. 39.35.00-3 Effective Date: July 1, 2018

Related medical policies:

- **Antihyperlipidemics – Apolipoprotein B Synthesis Inhibitors: lomitapide mesylate (JUXTAPID®)**

Note: *New-to-market drugs included in this class based on the Apple Health Preferred Drug List are non-preferred and subject to this prior authorization (PA) criteria. Non-preferred agents in this class require an inadequate response or documented intolerance due to severe adverse reaction or contraindication to at least TWO preferred agents. If there is only one preferred agent in the class documentation of inadequate response to ONE preferred agent is needed. If a drug within this policy receives a new indication approved by the Food and Drug Administration (FDA), medical necessity for the new indication will be determined on a case-by-case basis following FDA labeling.*

To see the list of the current Apple Health Preferred Drug List (AHPDL), please visit: https://www.hca.wa.gov/assets/billers-and-providers/apple-health-preferred-drug-list.xlsx

Background:

PCSK-9 is an enzyme that acts as part of the cholesterol homeostasis process in humans. PCSK-9 binds to the epidermal growth factor-like domain of the low-density lipoprotein (LDL) receptor on human hepatocytes. This binding forces LDL receptors to remain in the "open" confirmation, which facilitates their destruction, limiting the ability of the liver to remove LDL cholesterol from circulation. Humans with loss of function mutations in PCSK-9 have notable lower LDL cholesterol concentrations, and somewhat lower risk of cardiovascular disease.

Medical necessity

Drug	Medical Necessity
Evolocumab (**REPATHA®**) Alirocumab (**PRALUENT®**)	• PCSK-9 inhibitors may be considered medically necessary in patients who meet the criteria described in the clinical policy below. • If all criteria are not met, but there are documented medically necessary or situational circumstances, based on the professional judgement of the clinical reviewer, requests may be approved on a case-by-case basis up to the initial authorization duration. • Clients new to Apple Health or new to an MCO, who are requesting regimens for continuation of therapy should be reviewed following the reauthorization criteria listed below.

Clinical policy:

Clinical Criteria	
	1. Diagnosis of primary hypercholesterolemia **OR** heterozygous familial hypercholesterolemia defined by **ONE** of the following:

Primary Hypercholesterolemia/ Heterozygous Familial Hypercholesterolemia (HeFH)	a. Clinical diagnosis using diagnostic tools such as US MedPed, Simon Broome Register Group, or Dutch Lipid Panel; **OR** b. Genetic typing confirming presence of familial hypercholesterolemia genes; **AND** 2. Concomitant therapy with the highest-tolerated statin dose (see definitions below) and ezetimibe for at least 6 consecutive weeks **AND ONE** of the following: a. LDL has not achieved at least 50% reduction from baseline; **OR** b. Inability to achieve LDL cholesterol level <100mg/dL; **OR** c. For adults with known coronary heart disease or diabetes, inability to achieve LDL cholesterol level <70mg/dL; **AND** 3. For alirocumab greater than or equal to (≥) 18 years of age; **AND** 4. For evolocumab greater than or equal to (≥) 10 years of age; **AND** 5. **Not** used in combination with another PCSK-9 inhibitor; **AND** 6. For non-preferred products, trial and failure of greater than or equal to (≥) 1 preferred products **Approve for 6 months** If all criteria are not met, but there are documented medically necessary or situational circumstances, based on the professional judgement of the clinical reviewer, requests may be approved on a case-by-case basis up to the initial authorization duration. **Criteria (Reauthorization)** 1. Continues to receive the maximum tolerated dose of statin unless contraindicated or intolerant to statin therapy; **AND** 2. Documentation of continued clinical benefit, (e.g. at least a 30% reduction in LDL from initiation of PCSK-9 Inhibitor or achievement of patient-specific goal) **Approve for 12 months** If all criteria are not met, but there are documented medically necessary or situational circumstances, based on the professional judgement of the clinical reviewer, requests may be approved on a case-by-case basis up to the reauthorization duration.
Secondary Prophylaxis in Adults with Established Cardiovascular Disease (CVD)	1. History of clinical atherosclerotic cardiovascular diseases (ASCVD), including at least **ONE** of the following: a. Myocardial infarction (MI); **OR** b. Acute coronary syndrome (ACS); **OR** c. Angina; **OR** d. Transient ischemic attack (TIA); **OR** e. Cerebrovascular accident (CVA); **OR** f. Coronary revascularization procedures; **OR** g. Peripheral arterial disease (PAD); **AND**

	2. Concomitant therapy with the highest-tolerated statin dose (see definitions below) and ezetimibe for at least 6 consecutive weeks **AND** **ONE** of the following: a. LDL has not achieved at least 50% reduction from baseline; **OR** b. Inability to achieve LDL cholesterol level <70mg/dL; **AND** 3. Greater than or equal to (≥) 18 years of age; **AND** 4. **Not** used in combination with another PCSK-9 inhibitor; **AND** 5. For non-preferred products, trial and failure of greater than or equal to (≥) 1 preferred products **Approve for 6 months** If all criteria are not met, but there are documented medically necessary or situational circumstances, based on the professional judgement of the clinical reviewer, requests may be approved on a case-by-case basis up to the initial authorization duration. **Criteria (Reauthorization)** 1. Continues to receive the maximum tolerated dose of statin unless contraindicated or intolerant to statin therapy; **AND** 2. Documentation of continued clinical benefit, (e.g. at least a 30% reduction in LDL from initiation of PCSK-9 Inhibitor or achievement of patient-specific goal) **Approve for 12 months** If all criteria are not met, but there are documented medically necessary or situational circumstances, based on the professional judgement of the clinical reviewer, requests may be approved on a case-by-case basis up to the reauthorization duration.
Homozygous Familial Hypercholesterolemia (HoFH)	1. Clinical diagnosis of homozygous familial hypercholesterolemia defined by **ONE** of the following: a. History of untreated LDL ≥500mg/dL for adults, untreated LDL ≥400mg/dL for children, or treated LDL ≥300mg/dL for adults and children with **ONE** of the following: i. A xanthoma before 10 years of age; **OR** ii. Evidence of heterozygous familial hypercholesterolemia in both parents; **OR** b. Genetic typing confirming presence of familial hypercholesterolemia genes; **AND** 2. Concomitant therapy with the highest-tolerated statin dose (see definitions below) and ezetimibe for at least 6 consecutive weeks **AND** **ONE** of the following: a. LDL has not achieved at least 50% reduction from baseline; **OR** b. Inability to achieve LDL cholesterol level <100mg/dL for adults or <135mg/dL for children; **AND**

	3. For evolocumab, greater than or equal to (≥) 10 years of age; **AND** 4. For alirocumab, greater than or equal to (≥) 18 years of age; **AND** 5. **NONE** of the following: a. Used in combination with another PCSK-9 inhibitor; **AND** b. Used in combination with Juxtapid (lomitapide); **AND** 6. For non-preferred products, trial and failure of greater than or equal to (≥) 1 preferred products **Approve for 6 months** If all criteria are not met, but there are documented medically necessary or situational circumstances, based on the professional judgement of the clinical reviewer, requests may be approved on a case-by-case basis up to the initial authorization duration.
	Criteria (Reauthorization) 1. Continues to receive the maximum tolerated dose of statin unless contraindicated or intolerant to statin therapy; **AND** 2. Documentation of continued clinical benefit, (e.g. at least a 30% reduction in LDL from initiation of PCSK-9 Inhibitor or achievement of patient-specific goal) **Approve for 12 months** If all criteria are not met, but there are documented medically necessary or situational circumstances, based on the professional judgement of the clinical reviewer, requests may be approved on a case-by-case basis up to the reauthorization duration.

Dosage and quantity limits

Drug Name	Dose and Quantity Limits
Evolocumab (**REPATHA**®) 140mg	#2 syringes/pens per 28-days
Evolocumab (**REPATHA** ®) 420mg	Homozygous Familial Hypercholesteorlemia: #2 cartridges per 28-days Primary hypercholesterolemia, heterozygous familial hypercholesterolemia, & secondary prophylaxis in adults with established CVD: #1 cartridge per 28-days
Alirocumab (**PRALUENT**®) 75mg	#2 pens per 28-days
Alirocumab (**PRALUENT**®) 150mg	#2 pens per 28-days

Definitions

Term	Description
High-Intensity Statin Therapy	rosuvastatin 20mg or 40mg atorvastatin 80mg atorvastatin 40mg if down-titrating from atorvastatin 80mg due to intolerance symptoms

Highest-tolerated statin dose	1. Highest-tolerated statin dose is defined as **ONE** of the following: a. FDA labeled maximum dose for high-intensity statin therapy (e.g. atorvastatin 40 to 80mg and rosuvastatin 20 to 40mg) b. Client is adherent to a statin with documentation supporting intolerance to at least two other statins c. Treatment with statin therapy is contraindicated or not tolerated. i. Statin intolerance is defined below d. Clients who have statin intolerance are not required to use ezetimibe prior to a PCSK-9 inhibitor
Ezetimibe intolerance	1. Ezetimibe intolerance is defined as not being able to tolerate ezetimibe or it is contraindicated 2. Clients who have ezetimibe intolerance may be moved directly to a PCSK-9 inhibitor while on maximally tolerated statin
Lowest Starting Daily Doses (Statins)	rosuvastatin (Crestor®) 5mg atorvastatin 10mg simvastatin 10mg lovastatin 20mg pravastatin 40mg fluvastatin 40mg pitavastatin (Livalo®) 2mg
Statin Intolerance	Documented trial and failure of at least two statins after ruling out hypothyroidism, changes in physical activity and exercise, and potential drug-drug interactions, due to pre-specified intolerance symptoms [see below] that began or increased during statin therapy and stopped when statin therapy was discontinued. Qualification of at least two statins is: one statin must be at lowest starting daily dose [see above] and a different statin may be at any dose. If patient is on combination therapy, such as a fibrate or niacin, discontinuing fibrate or niacin while maintaining statin therapy is required to establish statin intolerance. Rhabdomyolysis determined to be caused by any statin at any dose, after ruling out all other potential causes including drug-drug interactions, will be considered as a contraindication to statins as a class. Patients with history of rhabdomyolysis caused by statins must be managed by, or in consultation with, a specialist, and may be considered eligible for PCSK-9 Inhibitors on a case-by-case basis.
Pre-Specified Intolerance Symptoms	Myopathy or myalgia (muscle pain, ache, or weakness without CK elevation) Myositis (muscle symptoms with increased CK levels)

Clinical Atherosclerotic Cardiovascular Disease (ASCVD)	Clinical ASCVD, for the purposes of this policy, include myocardial infarction (MI), acute coronary syndrome (ACS), angina, transient ischemic attack (TIA), cerebrovascular accident (CVA), coronary revascularization procedures, peripheral arterial disease (PAD)

References

1. Craig EM. Clinical Review BLA 125522 Repatha (evolocumab). Center for Drug Evaluation and Research (CDER). Food and Drug Administration (FDA). 2015 Aug 24.
2. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA, The National Lipid Association's Muscle Safety Expert Panel. An assessment by the Statin Muscle Safety Task Force: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S58-71.
3. Cho L, Rocco M, Colquhoun D, Sullivan D, Rosenson RS, Dent R, Xue A, Scott R, Wasserman SM, Stroes E. Design and rationale of the GAUSS-2 study trial: a double-blind, ezetimibe-controlled phase 3 study of the efficacy and tolerability of evolocumab (AMG 145) in subjects with hypercholesterolemia who are intolerant of statin therapy. Clin Cardiol. 2014 Mar;37(3):131-9.
4. Guyton JR, Bays HE, Grundy SM, Jacobson TA; The National Lipid Association Statin Intolerance Panel. An assessment by the Statin Intolerance Panel: 2014 update. J Clin Lipidol 2014; 8 (3 Suppl): S72-81.
5. Hopkins PN1, Toth PP, Ballantyne CM, Rader DJ. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011 Jun;5(3 Suppl):S9-17.
6. Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, McKenney JM, Grundy SM, Gill EA, Wild RA, Wilson DP, Brown WV. National lipid association recommendations for patient-centered management of dyslipidemia: part 1--full report. J Clin Lipidol. 2015 Mar-Apr;9(2):129-69.
7. Cuchel, M, Bruckert, E, Ginsberg, HN, et al. 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. European heart journal. 2014;35:2146-57. PMID: 25053660
8. Sabatine, MS, Giugliano, RP, Keech, AC, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. The New England journal of medicine. 2017 May 04;376(18):1713-22. PMID: 28304224
9. Repatha™ [prescribing Information]. Thousand Oaks, CA: Amgen; September 2015
10. Raal, FJ, Honarpour, N, Blom, DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):341-50. PMID: 25282520
11. Goldberg, AC, Hopkins, PN, Toth, PP, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. Journal of clinical lipidology. 2011;5:S1-8. PMID: 21600525
12. Robinson, JG. Management of familial hypercholesterolemia: a review of the recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Manag Care Pharm. 2013;19:139-49. PMID: 23461430
13. Nordestgaard, BG, Chapman, MJ, Humphries, SE, et al. 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. European heart journal. 2013;34:3478-90a. PMID: 23956253

14. Cannon, CP, Blazing, MA, Giugliano, RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. The New England journal of medicine. 2015 Jun 3. PMID: 26039521
15. Lloyd-Jones, DM, Morris, PB, Ballantyne, CM, et al. 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: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. Journal of the American College of Cardiology. 2016 Mar 28. PMID: 27046161
16. Nissen, SE, Stroes, E, Dent-Acosta, RE, et al. Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial. United States, 2016. p. 1580-90.
17. Moriarty, PM, Jacobson, TA, Bruckert, E, et al. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. Journal of clinical lipidology. 2014 Nov-Dec;8(6):554-61. PMID: 25499937
18. U.S. Food and Drug Administration. Advisory committee briefing document on alirocumab (BLA 125559). [cited 6/18/2015]; Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM449865.pdf.
19. Mampuya, WM, Frid, D, Rocco, M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. American heart journal. 2013 Sep;166(3):597-603. PMID: 24016512
20. Guyton, JR, Bays, HE, Grundy, SM, Jacobson, TA, The National Lipid Association Statin Intolerance, P. An assessment by the Statin Intolerance Panel: 2014 update. Journal of clinical lipidology. 2014 May-Jun;8(3 Suppl):S72-81. PMID: 24793444
21. Stroes, ES, Thompson, PD, Corsini, A, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. European heart journal. 2015 Feb 18. PMID: 25694464
22. Kemper, AR, Coeytaux, R, Sanders, GD, et al. Disease-Modifying Antirheumatic Drugs (DMARDs) in Children With Juvenile Idiopathic Arthritis (JIA). 2011. PMID: 22091470
23. Zetia [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; August 2013.
24. Marks, D, Thorogood, M, Neil, HA, Humphries, SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis. 2003;168:1-14. PMID: 12732381
25. Blom DJ, Harada-Shiba M, Rubba P, et al. Efficacy and Safety of Alirocumab in Adults With Homozygous Familial Hypercholesterolemia: The ODYSSEY HoFH Trial. J Am Coll Cardiol. 2020;76(2):131-142.
26. 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 hypercholesterolaemia. Eur Heart J. 2015;36(43):2996-3003.
27. Moriarty PM, Parhofer KG, Babirak SP, et al. Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis: the ODYSSEY ESCAPE trial. Eur Heart J. 2016;37(48):3588-3595.
28. Kastelein JJ, Akdim F, Stroes ES, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia [published correction appears in N Engl J Med. 2008 May 1;358(18):1977]. N Engl J Med. 2008;358(14):1431-1443.
29. Grundy S, Stone N, Bailey A, et al. 2018 AHA/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. 2019; 139:e1082-e1143.

History

Date	Action and Summary of Changes
12/16/2015	New Policy
04/18/2018	Re-review
12/06/2018	Remove Kynamro related Policy
10/02/2019	Edit Note
07/23/2020	Revised "Note" at top to reflect new language for preferred/non-preferred products. Revised medical necessity to reflect new indication for alirocumab; condensed indications and revised wording to be more consistent between the two available PCSK-9 inhibitors. Revised clinical criteria, adding requirement for trial of ezetimibe for heterozygous familial hypercholesterolemia and secondary prophylaxis of cardiovascular disease; revised LDL requirement to reflect updated clinical practice guidelines in secondary prophylaxis section; condensed "prevention of CVD and ASCVD" sections into one section as same criteria, renamed to "secondary prophylaxis of CVD." Updated references.
09/28/2020	Added information detailing which products are preferred/non-preferred.
10/21/2020	Approved by DUR Board
10/30/2020	Added clinical criteria to Secondary Prophylaxis in Adults with Established Cardiovascular Disease (CVD) for very high risk patients. Updated definitions to include specific information used to define very high risk patients.
01/26/2021	Revised policy finalized
09/21/2021	Updated clinical criteria to include Praluent for HoFH. "Medical Necessity" language, and "dosage and quantity limits" section. Updated LDL requirements for secondary prophylaxis.
10/01/2021	Updated highest-tolerated statin dose in definitions section to allow statin regimens that do not meet high-intensity statin therapy. Removed specialists as a requirement.
12/14/2021	Updated definitions section to define when ezetimibe is not required for authorization of a PCSK-9 inhibitor.
1/25/2022	Updated secondary prophylaxis in adults with established CVD to include cerebrovascular accident. Updated Repatha age requirements to incorporate recent FDA label.