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Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) Inhibitors Prior Authorization with Quantity Limit Program Summary

POLICY REVIEW CYCLE

Effective Date **Date of Origin**
01-01-2025

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Praluent® (alirocumab) Subcutaneous injection	To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease Adjunct to diet, alone or in combination with other low density lipoprotein cholesterol (LDL-C)- lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C Adjunct to other LDL-C-lowering therapies in adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C		1
Repatha® (evolocumab) Subcutaneous injection	In adults with established cardiovascular disease (CVD) to reduce the risk of myocardial infarction, stroke, and coronary revascularization Adjunct to diet, alone or in combination with other LDL-C-lowering therapies in adults with primary hyperlipidemia, including HeFH, to reduce LDL-C Adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C Adjunct to other LDL-C-lowering therapies in adults and pediatric patients aged 10 years and older with HoFH, to reduce LDL-C		2

See package insert for FDA prescribing information: https://dailymed.nlm.nih.gov/dailymed/index.cfm

CLINICAL RATIONALE

HeFH	Criteria have been developed to aid in diagnosing heterozygous familial hypercholesterolemia (HeFH). These include the Simon Broome Register criteria and Dutch Lipid Clinic Network criteria.(5) A definite diagnosis of HeFH according to Simon Broome diagnostic criteria requires one of the following:(3,5) • Total cholesterol >6.7 mmol/L or low-density lipoprotein cholesterol (LDL-C) >4.0 mmol/L in a child/young person, or >7.5 mmol/L or LDL-C >4.9 mmol/L in an adult (levels either pre-treatment or highest on treatment) and tendon xanthomas, or evidence of these signs in a first-degree relative (parent, sibling, child) or second-degree relative (e.g., grandparent, uncle, aunt) OR

- DNA-based evidence of an LDL-receptor mutation, familial defective Apo B-100, or a PCSK9 mutation

A possible diagnosis of HeFH according to Simon Broome diagnostic criteria requires the following:(3,5)

- Total cholesterol >6.7 mmol/L or low-density lipoprotein cholesterol (LDL-C) >4.0 mmol/L in a child/young person, or >7.5 mmol/L or LDL-C >4.9 mmol/L in an adult (levels either pre-treatment or highest on treatment) AND at least one of the following:
    - Family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative OR
    - Family history of raised total cholesterol: >7.5 mmol/L in adult first- or second-degree relative or >6.7 mmol/L in child, brother, or sister aged younger than 16 years

The Dutch Lipid Clinic Network criteria (World Health Organization, 1999) assign points based on personal and family medical history, clinical signs, LDL-C concentration and DNA testing. A score is attributed to each component; the higher the score, the higher the likelihood of the person having HeFH. A definitive diagnosis of HeFH can be made in patients with greater than 8 points. A probable diagnosis can be made in patients with 6-8 points. Although the Simon Broome Register criteria consider a molecular diagnosis as evidence for definite FH, the Dutch Lipid Clinic Network requires that at least one other criterion be met in addition to molecular diagnosis.(5,6)

Dutch Lipid Clinic Network criteria for diagnosis of HeFH:(6)

Family history	Points
• First-degree relative with known premature (men <55 years, women <60 years) coronary artery disease (CAD), OR • First-degree relative with known LDL-C >95th percentile and/or • First-degree relative with tendon xanthomata and/or arcus cornealis, OR • Children <18 years with LDL-C >95th percentile	1 2
Clinical history	
• Patient has premature (men <55 years, women <60 years) CAD • Patient has premature (men <55 years, women <60 years) cerebral or peripheral vascular disease	2 1
Physical examination	
• Tendinous xanthomata	6 4

	• Arcus cornealis before age 45 years	
	Cholesterol levels mg/dL (mmol/liter)	
	• LDL-C >330 mg/dL (>8.5) • LDL-C 250-329 mg/dL (6.5-8.4) • LDL-C 190-249 mg/dL (5.0-6.4) • LDL-C 155-189 mg/dL (4.0-4.9)	8 5 3 1
	DNA analysis	
	• Functional mutation in the LDLR, Apo-B, or PCSK9 gene	8
	Diagnosis (based on the total number of points obtained)	
	Definitive FH diagnosis: >8 points Probable FH diagnosis: 6-8 points Possible FH diagnosis: 3-5 points Unlikely FH diagnosis: 0 to 2 points	
HoFH	Homozygous familial hypercholesterolemia (HoFH) is a rare autosomal semi-dominant disease affecting males and females equally, characterized by markedly elevated levels of low-density lipoprotein cholesterol (LDL-C) from conception and accelerated atherosclerotic cardiovascular disease (ASCVD), often resulting in early death. Recent estimates indicate that about 30,000 people worldwide have HoFH but less than 5% are identified. Estimated global prevalence of HoFH by United Nations world region, based on 2020 population data and estimates of HoFH prevalence ranging from 1:250,000 to 1:360,000. Inadequate awareness and a disconnect between clinical diagnosis and interpretation of genetic results by health providers and payers contribute to underdiagnosis and undertreatment of HoFH. To address this, the European Atherosclerosis Society (EAS) has recently updated clinical guidance for HoFH care to improve education, early diagnosis, and improve cardiovascular health for patients with HoFH worldwide.(4) In 2014, the EAS statement on HoFH focused attention on this rare life-threatening disease which at the time had limited therapeutic options. The last decade has shown great progress in understanding the genetic complexity of HoFH, with new highly efficacious LDL-C-lowering therapies leading to improved survival and quality of life. The 2023 EAS consensus statement includes updated criteria for the clinical diagnosis of HoFH and the recommendation to prioritize phenotypic (clinically suspected in the absence of genetic data) features over genotype.(4) The EAS notes plasma LDL-C is the critical discriminator for clinical diagnosis of HoFH. The updated 2023 clinical criteria recommends an untreated LDL-C of >10 mmol/L (>400 mg/dL) is suggestive of HoFH requiring further investigation to confirm the diagnosis (including a detailed medical and family history and/or genetic testing). Additional criteria includes cutaneous or tendon xanthomas before age of 10 years and/or untreated elevated LDL-C levels consistent with HeFH in both parents (or in digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH). Due to the large variety of lipid-lowering treatments that these patients typically receive, the historic cut-offs for a treated LDL-C are likely now obsolete.(4) However, LDL-C criteria are not the sole guide to diagnosis, given the genetic complexity of HoFH and variability in LDL-C levels and clinical phenotype. The updated 2023 genetic criteria is genetic confirmation of bi-allelic pathogenic/likely pathogenic	

	variants on different chromosomes at the LDLR, ApoB, PCSK9, or LDLRAP1 genes or greater than or equal to 2 such variants at different loci. The benefits outweigh the limitations of genetic testing in HoFH with increased certainty of diagnosis and access to, use of, and compliance with appropriate treatment. A significant limitation of genetic testing has and continues to be accessibility and cost. Additionally, predicting individual phenotype and clinical response from genotype is not straightforward, and pathogenicity for many detected DNA variants cannot be definitively established. Some patients with phenotypic HoFH have only one or even no pathogenic variant detected, and some patients with bi-allelic pathogenic variants express HeFH but not HoFH phenotypically.(4) The LDL-C level (i.e., the phenotype) and not the presence of a genetic diagnosis drives therapeutic decisions. Combination lipid-lowering therapy, both pharmacologic intervention and lipoprotein apheresis (LA), is foundational, together with lifestyle measures (diet and smoking cessation). Patients should start on a high-intensity statin and ezetimibe rather than statin monotherapy, but most will require additional therapies to attain goal. Within 8 weeks PCSK9-directed therapy should be considered where available. Response to these treatments is dependent on LDL receptor (LDL-R) activity. If patients show >15% additional LDL-C reduction, PCSK9-directed therapy may be continued, but if response is poor, clinicians should consider stopping this therapy. While PCSK9 therapy is likely to reduce the risk of ASCVD events, LDL-C levels will remain substantially above recommended goals for most patients. Other options include LDL receptor–independent therapies (such as evinacumab or lomitapide) and/or LA. Lomitapide is noted to provide better control of LDL-C than LA. Preliminary findings from the Pan-European Project in HoFH including 75 patients with HoFH showed that lomitapide treatment for up to 9 years (median 19 months) resulted in more than half attaining at least 50% reduction from baseline in LDL-C at last visit, with less need for apheresis in a substantial proportion of patients. If LA, evinacumab, or lomitapide are not available, liver transplantation can be considered.(4) The National Organization for Rare Disorders (NORD) states that patients with HoFH should be initially started on statins with preference given to higher potency statins (atorvastatin or rosuvastatin) used at the maximal dose noting that statins can be relatively ineffective in HoFH. This is because the mechanism of action of statins normally "triggers" the liver to express additional LDL-Rs. In the most severe cases of HoFH, the LDL-R are completely inactive which makes this response futile. Statins can be effective in individuals with HoFH if there is some residual LDL-R activity, or if they have causal DNA variants in the APOB or PCSK9 genes. Patients with HoFH often require additional treatment strategies including lomitapide and evinacumab-dgnb (Evkeeza). Additional treatment options include LA or liver transplantation.(7) The American Heart Association (AHA) last released a scientific statement in 2015 for familial hypercholesterolemia that recommended lomitapide may be considered as step 4 in HoFH patients as part of a four-drug combination along with LA. Progression through each drug therapy step happens if the patient's LDL-C is above goal after 3 months of adherent treatment. Initial drug monotherapy is with a high-intensity statin (rosuvastatin or atorvastatin). Step 2 is combination therapy with ezetimibe, which progresses to a three-drug regimen that adds one of the following: PCSK9 inhibitors, colesevelam or other bile acid sequestrant, or niacin.(8)
ASCVD	The most recent 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of Blood Cholesterol states that clinical atherosclerotic cardiovascular disease (ASCVD) includes the following, all of atherosclerotic origin:(9) • Acute coronary syndrome (ACS) • History of myocardial infarction (MI) • Stable or unstable angina • Coronary or other arterial revascularization • Stroke • Transient ischemic attack (TIA)

	• Peripheral artery disease (PAD) including aortic aneurysm
Management	The 2022 American College of Cardiology (ACC) Consensus Decision Pathway was designed to address current gaps in care for LDL-C lowering to reducing ASCVD risk. This effort relies extensively on the evidence established by the 2013 ACC/AHA and 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, and provides further recommendations regarding the use of newer non-statin therapies. The key updates that the 2022 ACC Consensus Pathway recommends for patients with ASCVD on maximally tolerated statin therapy are a recommendation for a lower LDL-C threshold of 55 mg/dL(or non-HDL-C of 85 mg/dL) for adults with ASCVD at very high risk, and an LDL-C threshold of 70mg/dL (or non-HDL-C of 100 mg/dL) for adults with ASCVD not at very high risk when considering the addition of a non-statin therapy. If adults with clinical ASCVD at very high risk on a statin therapy for secondary prevention require >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial non-statin therapy.(13) The 2022 ACC Consensus Panel also released updated Expert Consensus Decision Pathways (ECDPs) to encourage clinicians to consider a range of important factors as they define treatment plans for their patients. Whenever appropriate, ECDPs seek to provide unified articulation of clinical practice guidelines, appropriate use criteria, and other related ACC clinical policy including when to consult a lipid specialist. Referral is recommended for patients with ASCVD and baseline LDL-C ≥190 mg/dL who did not achieve a reduction of LDL-C ≥50% and LDL-C <70 mg/dL (or non–HDL-C <100 mg/dL) on maximally tolerated statin therapy in combination with non-statin therapy (ezetimibe, PCSK9 inhibitors, bempedoic acid, and/or inclisiran).(13) The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol categorizes high intensity statin therapy as atorvastatin 40-80mg and rosuvastatin 20-40mg which provides an LDL-C lowering of greater than or equal to 50%.(9) The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol states the following regarding PCSK9 therapy:(9) • Primary severe hypercholesterolemia (LDL-C greater than or equal to 190 mg/dL [greater than or equal to 4.9 mmol/L]) ○ In patients 30-75 years of age with HeFH and with an LDL-C level of 100 mg/dL or higher (greater than or equal to 2.6 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered ○ In patients 40-75 years of age with an untreated LDL-C level of 220 mg/dL or higher (greater than or equal to 5.7 mmol/L) or an LDL-C that is greater than or equal to 130 mg/dL while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered • Secondary atherosclerotic cardiovascular disease (ASCVD) prevention ○ In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe The National Lipid Association (NLA) 2019 consensus statement identifies the following patients, who are already on maximally tolerated statin therapy, as most likely to benefit from PCSK9 therapy.(10)

	• Extreme high-risk (greater than or equal to 40% 10-year ASCVD risk on maximally tolerated statin therapy) with LDL-C greater than or equal to 70 mg/dL and either of the following:
	  ○ Extensive or active burden of ASCVD (i.e., polyvascular ASCVD, which affects all 3 vascular beds—coronary, cerebrovascular, and peripheral arterial; clinical peripheral arterial disease in addition to coronary and/or cerebrovascular disease; a clinical ASCVD event with multivessel coronary artery disease defined as greater than or equal to 40% stenosis in greater than or equal to 2 large vessels; or recurrent myocardial infarction within 2 years of the initial event) in the presence of adverse or poorly controlled cardiometabolic risk factors
	  ○ Extremely high-risk elevations in cardiometabolic factors with less-extensive ASCVD (i.e., HeFH, diabetes, LDL-C greater than or equal to 100 mg/dL, less than high–intensity statin therapy, chronic kidney disease, poorly controlled hypertension, high-sensitivity C-reactive protein greater than 3 mg/L, or metabolic syndrome, usually occurring with other extremely high–risk or very-high-risk characteristics), usually with other adverse or poorly controlled cardiometabolic risk factors present. Patients with ASCVD and HeFH or severe hyperlipidemia (SH) LDL-C greater than or equal to 220 mg/dL are an additional group of extremely high–risk patients, with greater than or equal to 45% 10- year ASCVD risk despite statin therapy. Statin-treated HeFH patients with coronary artery calcium (CAC) score greater than 100 Agatston units also have about a 45% 10-year ASCVD risk despite statin therapy
	• Very high-risk (30-39% 10-year ASCVD risk on maximally tolerated statin therapy) with LDL-C greater than or equal to 100 mg/dL and the following:
	  ○ Less-extensive clinical ASCVD (i.e., no polyvascular ASCVD, no clinical peripheral arterial disease, a prior ASCVD event greater than or equal to 2 years prior, and no coronary artery bypass grafting)
	  ○ Adverse or poorly controlled cardiometabolic risk factor(s) including age greater than or equal to 65 years, current smoking, chronic kidney disease, lipoprotein(a) greater than or equal to 37 nmol/L, high-sensitivity C-reactive protein 1–3 mg/L, metabolic syndrome with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease, usually in the presence of other adverse or poorly controlled cardiometabolic risk factors
	• High-risk (20-29% 10-year ASCVD risk on maximally tolerated statin therapy) with LDL-C greater than or equal to 130 mg/dL and either of the following:
	  ○ High-risk patients with ASCVD who have the following:
	  ▪ Less-extensive ASCVD
	  ▪ Well-controlled cardiometabolic risk factors (i.e., no diabetes, nonsmoker, on high-intensity statin with LDL-C less than 100 mg/dL, blood pressure less than 140/90 mm Hg, and C-reactive protein less than 1 mg/dL)
	  ○ Primary prevention patients with HeFH or SH LDL-C greater than or equal to 220 mg/dL and have the following:
	  ▪ No clinical ASCVD or CAC less than 100 Agatston units
	  ▪ Poorly controlled cardiometabolic risk factor
	
	CAC Agatston score in non-contrast CT can be used for patient risk classification for coronary heart disease:(11,12)
	
	• 0 CAC = no CAC, very low risk,
	• 1-99 CAC = mild CAC, mildly increased risk
	• 100 - 299 CAC = moderate CAC, moderately increased risk
	• greater than or equal to 300 CAC = moderate to severely increased risk

Safety	Praluent is contraindicated in patients with a history of a serious hypersensitivity reaction to alirocumab or any of the excipients in Praluent. Hypersensitivity vasculitis, angioedema, and hypersensitivity reactions requiring hospitalization have occurred.(1) Repatha is contraindicated in patients with a history of a serious hypersensitivity reaction to evolocumab or any of the excipients in Repatha. Serious hypersensitivity reactions including angioedema have occurred.(2)

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2	Repatha prescribing information. Amgen Inc. September 2021.
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POLICY AGENT SUMMARY PRIOR AUTHORIZATION

Target Brand Agent(s)	Target Generic Agent(s)	Strength	Targeted MSC	Available MSC	Final Age Limit	Preferred Status
Praluent	alirocumab subcutaneous solution auto-injector	150 MG/ML ; 75 MG/ML	M ; N ; O ; Y	N		
Repatha ; Repatha pushtronex system ; Repatha sureclick	evolocumab subcutaneous soln auto-injector ; evolocumab subcutaneous soln cartridge/infusor ; evolocumab subcutaneous soln prefilled syringe	140 MG/ML ; 420 MG/3.5ML	M ; N ; O ; Y	N		

POLICY AGENT SUMMARY QUANTITY LIMIT

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	QL Amount	Dose Form	Day Supply	Duration	Addtl QL Info	Allowed Exceptions	Targeted NDCs When Exclusions Exist
Praluent	Alirocumab Subcutaneous Solution Auto-Injector 150 MG/ML	150 MG/ML	2	Pens	28	DAYS			
Praluent	Alirocumab Subcutaneous Solution Auto-Injector 75 MG/ML	75 MG/ML	2	Pens	28	DAYS			
Repatha	Evolocumab Subcutaneous Soln Prefilled Syringe 140 MG/ML	140 MG/ML	6	Syringes	28	DAYS			
Repatha pushtronex system	Evolocumab Subcutaneous Soln Cartridge/Infusor 420 MG/3.5ML	420 MG/3.5 ML	2	Systems	28	DAYS			
Repatha sureclick	Evolocumab Subcutaneous Soln Auto-Injector 140 MG/ML	140 MG/ML	6	Pens	28	DAYS			

CLIENT SUMMARY – PRIOR AUTHORIZATION

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Praluent	alirocumab subcutaneous solution auto-injector	150 MG/ML ; 75 MG/ML	Commercial ; HIM ; ResultsRx
Repatha ; Repatha pushtronex system ; Repatha sureclick	evolocumab subcutaneous soln auto-injector ; evolocumab subcutaneous soln cartridge/infusor ; evolocumab subcutaneous soln prefilled syringe	140 MG/ML ; 420 MG/3.5ML	Commercial ; HIM ; ResultsRx

CLIENT SUMMARY – QUANTITY LIMITS

Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Client Formulary
Praluent	Alirocumab Subcutaneous Solution Auto-Injector 150 MG/ML	150 MG/ML	Commercial ; HIM ; ResultsRx
Praluent	Alirocumab Subcutaneous Solution Auto-Injector 75 MG/ML	75 MG/ML	Commercial ; HIM ; ResultsRx
Repatha	Evolocumab Subcutaneous Soln Prefilled Syringe 140 MG/ML	140 MG/ML	Commercial ; HIM ; ResultsRx
Repatha pushtronex system	Evolocumab Subcutaneous Soln Cartridge/Infusor 420 MG/3.5ML	420 MG/3.5ML	Commercial ; HIM ; ResultsRx
Repatha sureclick	Evolocumab Subcutaneous Soln Auto-Injector 140 MG/ML	140 MG/ML	Commercial ; HIM ; ResultsRx

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	

Preferred Target Agent(s)	Non-Preferred Target Agent(s)
Repatha (evolocumab)	Praluent (alirocumab)

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The patient has a diagnosis of homozygous familial hypercholesterolemia (HoFH) and ALL of the following:
      1. The patient has a diagnosis of HoFH confirmed by ONE of the following:
         A. Genetic confirmation of bi-allelic pathogenic/likely pathogenic variants on different chromosomes at the *LDLR, Apo-B, PCSK9,* or *LDLRAP1* genes, or greater than or equal to 2 such variants at different loci **OR**
         B. History of untreated LDL-C greater than 400 mg/dL (greater than 10 mmol/L) and ONE of the following:
            1. The patient had cutaneous or tendon xanthomas before age of 10 years **OR**
            2. Untreated elevated LDL-C levels consistent with heterozygous FH in both parents, (or in digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH) **AND**
      2. ONE of the following:
         A. The patient has tried a high-intensity statin (e.g., atorvastatin 40-80 mg, rosuvastatin 20-40 mg daily) for 2 months and had an inadequate response **OR**
         B. The patient has an intolerance or hypersensitivity to ALL high-intensity statins **OR**
         C. The patient has an FDA labeled contraindication to ALL high-intensity statins **AND**
      3. The patient will use other lipid-lowering therapy (e.g., statin, ezetimibe, lipoprotein apheresis, lomitapide, evinacumab) **OR**
   B. BOTH of the following:
      1. ONE of the following:
         A. The patient has a diagnosis of heterozygous familial hypercholesterolemia (HeFH) **AND** ONE of the following:
            1. Genetic confirmation of one mutant allele at the *LDLR, Apo-B, PCSK9*, or *1/LDLRAP1* gene **OR**

Module	Clinical Criteria for Approval
	2. Pre-treatment LDL-C greater than 190 mg/dL (greater than 4.9 mmol/L) **OR** 3. The patient has clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, corneal arcus) **OR** 4. The patient has "definite" or "possible" familial hypercholesterolemia as defined by the Simon Broome criteria **OR** 5. The patient has a Dutch Lipid Clinic Network Criteria score of greater than 5 **OR** 6. The patient has a treated LDL-C level greater than or equal to 100 mg/dL after statin treatment with or without ezetimibe **OR** B. The patient has a diagnosis of clinical atherosclerotic cardiovascular disease (ASCVD) AND has ONE of the following: 1. Acute coronary syndrome 2. History of myocardial infarction 3. Stable or unstable angina 4. Coronary or other arterial revascularization 5. Stroke 6. Transient ischemic attack 7. Peripheral arterial disease, including aortic aneurysm, presumed to be of atherosclerotic origin **OR** C. The patient has a diagnosis of primary hyperlipidemia AND ONE of the following: 1. The patient has a coronary artery calcium or calcification (CAC) score greater than or equal to 300 Agatston units **OR** 2. The patient has a pre-treatment LDL-C level greater than or equal to 190 mg/dL (greater than or equal to 4.9 mmol/L) **OR** D. The patient has at least a 20% 10-year ASCVD risk AND ONE of the following: 1. The patient has greater than or equal to 40% 10-year ASCVD risk AND BOTH of the following: A. LDL-C greater than or equal to 70 mg/dL while on maximally tolerated statin therapy **AND** B. ONE of the following: 1. The patient has extensive or active burden of ASCVD (i.e., polyvascular ASCVD, which affects all 3 vascular beds—coronary, cerebrovascular, and peripheral arterial; clinical peripheral arterial disease in addition to coronary and/or cerebrovascular disease; a clinical ASCVD event with multivessel coronary artery disease defined as greater than or equal to 40% stenosis in greater than or equal to 2 large vessels; or recurrent myocardial infarction within 2 years of the initial event) in the presence of adverse or poorly controlled cardiometabolic risk factors **OR** 2. Extremely high-risk elevations in cardiometabolic factors with less-extensive ASCVD (i.e., diabetes, LDL-C greater than or equal to 100 mg/dL, less than high–intensity statin therapy, chronic kidney disease, poorly controlled hypertension, high-sensitivity C-reactive protein greater than 3 mg/L, or metabolic syndrome, usually occurring with other

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	extremely high–risk or very-high-risk characteristics), usually with other adverse or poorly controlled cardiometabolic risk factors present. **OR** 3. Patients with ASCVD and LDL-C greater than or equal to 220 mg/dL with greater than or equal to 45% 10- year ASCVD risk despite statin therapy **OR** 2. The patient has 30-39% 10-year ASCVD risk AND ALL of the following: A. LDL-C greater than or equal to 100 mg/dL while on maximally tolerated statin therapy **AND** B. Less-extensive clinical ASCVD (i.e., no polyvascular ASCVD, no clinical peripheral arterial disease, a prior ASCVD event greater than or equal to 2 years prior, and no coronary artery bypass grafting) **AND** C. Adverse or poorly controlled cardiometabolic risk factor(s) including age 65 years or older, current smoking, chronic kidney disease, lipoprotein(a) greater than or equal to 37 nmol/L, high-sensitivity C-reactive protein 1–3 mg/L, metabolic syndrome with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease, usually in the presence of other adverse or poorly controlled cardiometabolic risk factors **OR** 3. The patient has 20-29% 10-year ASCVD risk AND BOTH of the following: A. LDL-C greater than or equal to 130 mg/dL while on maximally tolerated statins **AND** B. ONE of the following: 1. The patient has less extensive ASCVD and well-controlled cardiometabolic risk factors (i.e., no diabetes, nonsmoker, on high-intensity statin with LDL-C less than 100 mg/dL, blood pressure less than 140/90 mm Hg, and C-reactive protein less than 1 mg/dL) **OR** 2. The use is for primary prevention with LDL-C greater than or equal to 220 mg/dL AND BOTH of the following: A. No clinical ASCVD or CAC less than 100 Agatston units **AND** B. Poorly controlled cardiometabolic risk factor **AND** 2. ONE of the following: A. The patient has been adherent to high-intensity statin therapy (i.e., atorvastatin 40-80mg, rosuvastatin 20-40 mg daily) for at least 8 consecutive weeks AND ONE of the following: 1. The patient's LDL-C level after this statin therapy remains greater than or equal to 70 mg/dL **OR** 2. The patient has not achieved a 50% reduction in LDL-C from this statin therapy **OR** 3. If the patient has ASCVD at very high risk, ONE of the following: A. The patient's LDL-C level after this statin therapy remains greater than or equal to 55 mg/dL **OR** B. The patient's non HDL-C level after this statin therapy remains greater than or equal to 85 mg/dL **OR**

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	B. The patient has been determined to be statin intolerant by meeting ONE of the following: 1. The patient experienced statin-related rhabdomyolysis **OR** 2. The patient experienced skeletal-related muscle symptoms (e.g., myopathy, myalgia) and BOTH of the following: A. The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin AND rosuvastatin **AND** B. When receiving separate trials of both atorvastatin and rosuvastatin, the skeletal-related muscle symptoms resolved upon discontinuation of each statin **OR** 3. The patient experienced elevations in hepatic transaminase while receiving separate trials of both atorvastatin and rosuvastatin **OR** C. The patient has a hypersensitivity to atorvastatin AND rosuvastatin **OR** D. The patient has an FDA labeled contraindication to atorvastatin AND rosuvastatin **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **OR** D. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The patient will NOT be using the requested agent in combination with another PCSK9 agent for the requested indication **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. If the client has preferred agent(s), then ONE of the following: A. The requested agent is a preferred agent **OR** B. The patient has tried and had an inadequate response to the preferred agent **OR** C. The patient has an intolerance or hypersensitivity to the preferred agent **OR** D. The patient has an FDA labeled contraindication to ALL preferred agents **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for therapy for PCSK9 inhibitors through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. If the client has preferred agent(s), then ONE of the following: A. The requested agent is a preferred agent **OR** B. The patient has tried and had an inadequate response to the preferred agent **OR** C. The patient has an intolerance or hypersensitivity to the preferred agent **OR** D. The patient has an FDA labeled contraindication to ALL preferred agents **AND** 3. The patient has shown clinical benefit with a PCSK9 inhibitor **AND** 4. The patient is currently adherent to therapy with a PCSK9 inhibitor **AND**

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	5. If the patient has a diagnosis of HoFH, they will continue to use other lipid-lowering therapy (e.g., statin, ezetimibe, lipoprotein apheresis, lomitapide, evinacumab) **AND** 6. If the patient has ASCVD, HeFH, or hyperlipidemia, then ONE of the following: A. The patient is currently adherent to high-intensity statin therapy (i.e., atorvastatin 40-80mg, rosuvastatin 20-40 mg daily) **OR** B. The patient has been determined to be statin intolerant by meeting ONE of the following criteria: 1. The patient experienced statin-related rhabdomyolysis **OR** 2. The patient experienced skeletal-related muscle symptoms (e.g., myopathy, myalgia) and BOTH of the following: A. The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin AND rosuvastatin **AND** B. When receiving separate trials of both atorvastatin and rosuvastatin the skeletal-related muscle symptoms resolved upon discontinuation of each statin **OR** 3. The patient experienced elevations in hepatic transaminase while receiving separate trials of both atorvastatin and rosuvastatin **OR** C. The patient has a hypersensitivity to atorvastatin AND rosuvastatin **OR** D. The patient has an FDA labeled contraindication to atorvastatin AND rosuvastatin **AND** 7. The patient will NOT be using the requested agent in combination with another PCSK9 agent for the requested indication **AND** 8. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

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Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months