Antihyperlipidemics –
Proprotein Converatase Subtilisin Kexin type 9 (PCSK-9) Inhibitors

WA.PHAR.39 Antihyperlipidemics PCSK9 Inhibitors

Related medical policies:

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

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 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-C concentrations, and somewhat lower risk of cardiovascular disease.

Medical necessity

Drug	Medical Necessity
Alirocumab (**PRALUENT®**)	Alirocumab may be considered medically necessary when: • Used for the treatment of primary heterozygous familial hypercholesterolemia or clinical artherosclerotic cardiovascular disease
Evolocumab (**REPATHA®**)	Evolocumab may be considered medically necessary when: • Used for the treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) • Used for the treatment of homozygous familial hypercholesterolemia (HoFH) • Used for the treatment of atherosclerotic cardiovascular disease (ASCVD) • Used to reduce risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease (CVD)

Clinical policy:

Drug	Clinical Criteria (Initial Approval)
Alirocumab (**PRALUENT®**)	**For <u>Heterozygous Familial Hypercholesterolemia (HeFH)</u>** 1. Diagnosis of Heterozygous Familial Hypercholesterolemia defined by **ONE** of the following: a. Clinical diagnosis using diagnostic tools such as US MedPed, Simon Broome Register Group, or Dutch Lipid Panel

b. Age ≥20 and LDL ≥190mg/dL on maximally tolerated statin therapy prior to adding a PCSK9 Inhibitor
c. Age <20 and LDL ≥160mg/dL on maximally tolerated statin therapy prior to adding a PCSK9 Inhibitor
d. Genetic typing confirming presence of familial hypercholesterolemia genes

2. Concomitant therapy with the highest-tolerated statin regimen for at least 6 consecutive weeks; **AND** LDL has not achieved at least 50% reduction from baseline or remains ≥100mg/dL
    a. Highest-tolerated dose is defined as **ONE** of the following:
        i. FDA labeled maximum dose for high-intensity statin therapy (e.g. atorvastatin 40 to 80mg and rosuvastatin 20 to 40mg)
        ii. Treatment with maximally tolerated statin therapy has been ineffective, contraindicated, or not tolerated.
            1. A statin is considered ineffective if patients are not able to tolerate high-intensity or have not had an LDL-C reduction of at least 50% while on a maximally tolerated dose of statin with or without concurrent trial of ezetimibe for at least 6 weeks.
            2. Statin intolerance is defined as the inability to tolerate at least two different statin medications at the lowest FDA-approved starting dose when other potential causes of muscle symptoms have been maximally managed or ruled out
3. Greater than or equal to (≥) 18 years of age
4. Prescribed by or in consultation with a provider specializing in lipid management (e.g. cardiologist, lipid specialist, or endocrinologist)
5. **NONE** of the following:
    a. Used in combination with another proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor
    b. Used in combination with Kynamro (mipomersen)

Approve for 6 months

Criteria (Reauthorization)

1. Continues to receive the maximum tolerated dose of statin unless contraindicated or intolerant to statin therapy
2. Documentation of continued clinical benefit, (e.g. at least a 30% reduction in LDL from initiation of PCSK9 Inhibitor or achievement of patient-specific goal)

Approve for 12 months

Clinical Criteria (Initial Approval)

	For <u>Primary Hypercholesterolemia with Atherosclerotic Cardiovascular Disease (ASCVD):</u> 1. History of clinical atherosclerotic cardiovascular diseases (ASCVD), including at least **ONE** of the following: a. myocardial infarction (MI), presumed to be of atherosclerotic origin b. acute coronary syndrome (ACS), presumed to be of atherosclerotic origin c. severe angina, presumed to be of atherosclerotic origin d. stroke, presumed to be of atherosclerotic origin e. transient ischemic attack (TIA), presumed to be of atherosclerotic origin f. coronary revascularization procedures, presumed to be of atherosclerotic origin g. peripheral arterial disease, presumed to be of atherosclerotic origin 2. Concomitant therapy with the highest-tolerated statin regimen for at least 6 consecutive weeks; **AND** LDL has not achieved at least 50% reduction from baseline or remains ≥100mg/dL a. Highest-tolerated dose is defined as **ONE** of the following: i. FDA labeled maximum dose for high-intensity statin therapy (e.g. atorvastatin 40 to 80mg and rosuvastatin 20 to 40mg) ii. Treatment with maximally tolerated statin therapy has been ineffective, contraindicated, or not tolerated. 1. A statin is considered ineffective if patients are not able to tolerate high-intensity or have not had an LDL-C reduction of at least 50% while on a maximally tolerated dose of statin with or without concurrent trial of ezetimibe for at least 6 weeks. 2. Statin intolerance is defined as the inability to tolerate at least two different statin medications at the lowest FDA-approved starting dose when other potential causes of muscle symptoms have been maximally managed or ruled out 3. Greater than or equal to (≥) 18 years of age 4. Prescribed by or in consultation with a provider specializing in lipid management (e.g. cardiologist, lipid specialist, or endocrinologist) 5. **NONE** of the following: a. Used in combination with another proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor b. Used in combination with Kynamro (mipomersen) **Approve for 6 months**

	Criteria (Reauthorization) 1. Continues to receive the maximum tolerated dose of statin unless contraindicated or intolerant to statin therapy 2. Documentation of continued clinical benefit, (e.g. at least a 30% reduction in LDL from initiation of PCSK9 Inhibitor or achievement of patient-specific goal) **Approve for 12 months**
Drug	**Clinical Criteria (Initial Approval)**
Evolocumab (**REPATHA®**)	**For <u>Heterozygous Familial Hypercholesterolemia (HeFH)</u>** 1. Diagnosis of Heterozygous Familial Hypercholesterolemia defined by **ONE** of the following: a. Clinical diagnosis using diagnostic tools such as US MedPed, Simon Broome Register Group, or Dutch Lipid Panel b. Age ≥20 and LDL ≥190mg/dL on maximally tolerated statin therapy prior to adding a PCSK9 Inhibitor c. Age <20 and LDL ≥160mg/dL on maximally tolerated statin therapy prior to adding a PCSK9 Inhibitor d. Genetic typing confirming presence of familial hypercholesterolemia genes 2. Concomitant therapy with the highest-tolerated statin regimen for at least 6 consecutive weeks; **AND** LDL has not achieved at least 50% reduction from baseline or remains ≥100mg/dL a. Highest-tolerated dose is defined as **ONE** of the following: i. FDA labeled maximum dose for high-intensity statin therapy (e.g. atorvastatin 40 to 80mg and rosuvastatin 20 to 40mg) ii. Treatment with maximally tolerated statin therapy has been ineffective, contraindicated, or not tolerated. 1. A statin is considered ineffective if patients are not able to tolerate high-intensity or have not had an LDL-C reduction of at least 50% while on a maximally tolerated dose of statin with or without concurrent trial of ezetimibe for at least 6 weeks. 2. Statin intolerance is defined as the inability to tolerate at least two different statin medications at the lowest FDA-approved starting dose when other potential causes of muscle symptoms have been maximally managed or ruled out 3. Greater than or equal to (≥) 18 years of age 4. Prescribed by or in consultation with a provider specializing in lipid management (e.g. cardiologist, lipid specialist, or endocrinologist) 5. **NONE** of the following:

a. Used in combination with another proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor
b. Used in combination with Kynamro (mipomersen)

Approve for 6 months

Criteria (Reauthorization)

1. Continues to receive the maximum tolerated dose of statin unless contraindicated or intolerant to statin therapy
2. Documentation of continued clinical benefit, (e.g. at least a 30% reduction in LDL from initiation of PCSK9 Inhibitor or achievement of patient-specific goal)

Approve for 12 months

Clinical Criteria (Initial Approval)

For <u>Primary Hypercholesterolemia with Atherosclerotic Cardiovascular Disease (ASCVD):</u>

1. History of clinical atherosclerotic cardiovascular diseases (ASCVD), including at least **ONE** of the following:
    a. myocardial infarction (MI), presumed to be of atherosclerotic origin
    b. acute coronary syndrome (ACS), presumed to be of atherosclerotic origin
    c. severe angina, presumed to be of atherosclerotic origin
    d. stroke, presumed to be of atherosclerotic origin
    e. transient ischemic attack (TIA), presumed to be of atherosclerotic origin
    f. coronary revascularization procedures, presumed to be of atherosclerotic origin
    g. peripheral arterial disease, presumed to be of atherosclerotic origin
2. Concomitant therapy with the highest-tolerated statin regimen for at least 6 consecutive weeks; **AND** LDL has not achieved at least 50% reduction from baseline or remains ≥100mg/dL
    a. Highest-tolerated dose is defined as **ONE** of the following:
        i. FDA labeled maximum dose for high-intensity statin therapy (e.g. atorvastatin 40 to 80mg and rosuvastatin 20 to 40mg)
        ii. Treatment with maximally tolerated statin therapy has been ineffective, contraindicated, or not tolerated.
            1. A statin is considered ineffective if patients are not able to tolerate high-intensity or have not had an LDL-C reduction of at least 50% while on a maximally tolerated dose of statin with or without concurrent trial of ezetimibe for at least 6 weeks.

2. Statin intolerance is defined as the inability to tolerate at least two different statin medications at the lowest FDA-approved starting dose when other potential causes of muscle symptoms have been maximally managed or ruled out
3. Greater than or equal to (≥) 18 years of age
4. Prescribed by or in consultation with a provider specializing in lipid management (e.g. cardiologist, lipid specialist, or endocrinologist)
5. **NONE** of the following:
    a. Used in combination with another proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor
    b. Used in combination with Kynamro (mipomersen)

Approve for 6 months

Criteria (Reauthorization)

1. Continues to receive the maximum tolerated dose of statin unless contraindicated or intolerant to statin therapy
2. Documentation of continued clinical benefit, (e.g. at least a 30% reduction in LDL from initiation of PCSK9 Inhibitor or achievement of patient-specific goal)

Approve for 12 months

For <u>Homozygous Familial Hypercholesterolemia (HoFH):</u>

1. Clinical diagnosis of Homozygous Familial Hypercholesterolemia defined by **ONE** of the following:
    a. history of untreated LDL ≥500mg/dL with either a xanthoma before 10 years of age
    b. evidence of heterozygous familial hypercholesterolemia in both parents;
    c. genetic typing confirming presence of Familial Hypercholesterolemia genes
2. Concomitant therapy with the highest-tolerated statin regimen for at least 6 consecutive weeks or is statin intolerant; AND LDL remains ≥130mg/dL
    a. Highest-tolerated dose is defined as ONE of the following:
        i. FDA labeled maximum dose for high-intensity statin therapy (e.g. atorvastatin 40 to 80mg and rosuvastatin 20 to 40mg)
        ii. Treatment with maximally tolerated statin therapy has been ineffective, contraindicated, or not tolerated.
            1. A statin is considered ineffective if patients are not able to tolerate high-intensity or have not had an LDL-C reduction of at least 50% while on a maximally tolerated dose of

statin with or without concurrent trial of ezetimibe for at least 6 weeks.

2. Statin intolerance is defined as the inability to tolerate at least two different statin medications at the lowest FDA-approved starting dose when other potential causes of muscle symptoms have been maximally managed or ruled out

3. Greater than or equal to (≥) 13 years of age
4. Prescribed by or in consultation with a cardiologist, endocrinologist or lipid specialist
5. **NONE** of the following:
    a. Used in combination with another proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor
    b. Used in combination with Juxtapid (lomitapide)
    c. Used in combination with Kynamro (mipomersen)

Approve for 6 months

Criteria (Reauthorization)

1. Continues to receive the maximum tolerated dose of statin unless contraindicated or intolerant to statin therapy
2. Documentation of continued clinical benefit, (e.g. at least a 30% reduction in LDL from initiation of PCSK9 Inhibitor or achievement of patient-specific goal)

Approve for 12 months

For <u>reducing the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease (CVD):</u>

1. Established cardiovascular diseases (CVD), including at least **ONE** of the following:
    a. myocardial infarction (MI), presumed to be of atherosclerotic origin
    b. acute coronary syndrome (ACS), presumed to be of atherosclerotic origin
    c. severe angina, presumed to be of atherosclerotic origin
    d. stroke, presumed to be of atherosclerotic origin
    e. transient ischemic attack (TIA), presumed to be of atherosclerotic origin
    f. coronary revascularization procedures, presumed to be of atherosclerotic origin
    g. peripheral arterial disease, presumed to be of atherosclerotic origin

2. Concomitant therapy with the highest-tolerated statin regimen for at least 6 consecutive weeks; **AND** LDL has not achieved at least 50% reduction from baseline or remains ≥100mg/dL
    a. Highest-tolerated dose is defined as **ONE** of the following:
        i. FDA labeled maximum dose for high-intensity statin therapy (e.g. atorvastatin 40 to 80mg and rosuvastatin 20 to 40mg)
        ii. Treatment with maximally tolerated statin therapy has been ineffective, contraindicated, or not tolerated.
            1. A statin is considered ineffective if patients are not able to tolerate high-intensity or have not had an LDL-C reduction of at least 50% while on a maximally tolerated dose of statin with or without concurrent trial of ezetimibe for at least 6 weeks.
            2. Statin intolerance is defined as the inability to tolerate at least two different statin medications at the lowest FDA-approved starting dose when other potential causes of muscle symptoms have been maximally managed or ruled out
3. Greater than or equal to (≥) 18 years of age
4. Prescribed by or in consultation with a cardiologist, endocrinologist or lipid specialist
5. **NONE** of the following:
    a. Used in combination with another proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor
    b. Used in combination with Juxtapid (lomitapide)
    c. Used in combination with Kynamro (mipomersen)

Approve for 6 months

Criteria (Reauthorization)

1. Continues to receive the maximum tolerated dose of statin unless contraindicated or intolerant to statin therapy
2. Documentation of continued clinical benefit, (e.g. at least a 30% reduction in LDL from initiation of PCSK9 Inhibitor or achievement of patient-specific goal)

Approve for 12 months

Dosage and quantity limits

Drug Name	Dose and Quantity Limits
Evolocumab (**REPATHA**®) 140mg	#2 syringes/pens per 28-days
Evolocumab (**REPATHA** ®) 420mg	#1 pens per 28-days
Alirocumab (**PRALUENT**®) 75mg	#2 syringes/pens per 28-days

Definitions

Term	Description
High-Intensity Statin Therapy	rosuvastatin (Crestor®) 20mg or 40mg atorvastatin 80mg atorvastatin 40mg if down-titrating from atorvastatin 80mg due to intolerance symptoms
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 below] and a different statin may be at any dose. If patient is on combination therapy, such as a fibrate or niacin, tapering of 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 lipid specialists, and may be considered eligible for PCSK9 Inhibitors on a case-by-case basis. Patients who have failed to meet criterion 3 in medical policy may be managed on non-daily statin therapy if able to demonstrate that they are on maximally-tolerated therapy and can maintain dose while on PCSK9 Inhibitor.
Pre-Specified Intolerance Symptoms	Myopathy or myalgia (muscle pain, ache, or weakness without CK elevation) Myositis (muscle symptoms with increased CK levels)
Diagnosis of ASCVD	Acute coronary syndrome, or a history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease presumed to be of atherosclerotic origin

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