PCSK9 Inhibitors

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

This policy document describes the status of medical technology or treatment at the time the document was developed. Since that time, new technology or treatment may have emerged or new medical literature may have been published. This policy will be reviewed regularly and be updated as scientific and medical literature becomes available.

DESCRIPTION

The intent of the PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) Inhibitor drug policy is to ensure appropriate selection of patients for therapy based on product labeling, clinical guidelines and clinical studies. Repatha® (evolocumab) and Praluent® (alirocumab) are both Food and Drug Administration (FDA) indicated as an adjunct to diet and maximally tolerated statin therapy for both the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) and adults with clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). In addition, Repatha received approval for the treatment of patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis).

POLICY

I. Repatha® (evolocumab) may be considered medically necessary for the treatment of clinical atherosclerotic cardiovascular disease ASCVD (acute coronary syndrome, history of myocardial infarction, stable or unstable angina, coronary or arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease that is atherosclerotic in origin) when the following criteria are met:
   • Patient is 18 years of age or older
   • Patient is engaging in healthy lifestyle changes including a low-fat diet (saturated fat <7% of total calories) and exercise program (150 minutes or more of moderate to vigorous intensity physical activity per week, or engaging as medically appropriate) demonstrated by notable improvement in body mass index (BMI)*, or other clinical indicators of progress (e.g., improvements in fasting blood glucose, lipid profile, exercise tolerability) documented in the medical record
   • Patient has been unable to achieve an LDL-C reduction of ≥ 50% despite adherence† to the combination of lifestyle changes and at least three months of lipid lowering therapy:
     ○ BOTH high-intensity statins (atorvastatin 80 mg and rosuvastatin 40 mg) in combination with ezetimibe, OR
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II. **Praluent (alirocumab)** may be considered medically necessary for the treatment of clinical atherosclerotic cardiovascular disease ASCVD (acute coronary syndrome, history of myocardial infarction, stable or unstable angina, coronary or arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease that is atherosclerotic in origin) when the following criteria are met:

- Patient is 18 years of age or older
- Patient is engaging in healthy lifestyle changes including a low-fat diet (saturated fat <7% of total calories) and exercise program (150 minutes or more of moderate to vigorous intensity physical activity per week, or engaging as medically appropriate) demonstrated by notable improvement in body mass index (BMI)*, or other clinical indicators of progress (e.g., improvements in fasting blood glucose, lipid profile, exercise tolerability), documented in the medical record
- Patient has been unable to achieve an LDL-C reduction of ≥ 50% despite adherence† to the combination of lifestyle changes and at least three months of lipid lowering therapy:
  - BOTH high-intensity statins (atorvastatin 80 mg and rosuvastatin 40 mg) in combination with ezetimibe, OR
  - TWO moderate intensity statins (e.g. pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin 80 mg, pitavastatin 2-4 mg, simvastatin 20-40 mg) in combination with ezetimibe, only in the event the patient is unable to complete either of the high-intensity statin trials at the maximum approved dosing
- OR
- Patient has a documented contraindication (e.g., active liver disease, pregnancy, breastfeeding), or medically justifiable reason that precludes statin use (e.g. patient has experienced rhabdomyolysis, CK elevations ≥ 10x ULN, or statin intolerance).
  - Statin intolerance shall be defined in accordance with the National Lipid Association definition:
    - Inability to tolerate at least two statins (one at any dose, one at lowest daily dose) due to objectionable symptoms or abnormal biomarkers temporally related to statin use, reversible upon statin discontinuation and reproducible by re-challenge while excluding other known determinants. Other known determinants include low body mass index (BMI), acute infection, untreated or undertreated hypothyroidism, severe renal or hepatic dysfunction, organ transplant, recent severe trauma, HIV infection, Vitamin D deficiency, history of creatine kinase elevation, history of preexisting or unexplained muscle or joint pain, high level of physical activity, illicit drug abuse, excess alcohol use. Each statin trial, both initial and re-challenge shall be at least two weeks duration.
    - One statin at lowest starting daily dose
      - Rosuvastatin 5mg
      - Atorvastatin 10mg
      - Simvastatin 10mg
      - Lovastatin 20mg
      - Pravastatin 40mg
      - Fluvastatin 40mg
      - Pitavastatin 2mg
    - One statin at any daily dose
      - Patient’s current triglyceride level is less than 400 mg/dL
      - Repatha will be added to statin therapy unless a contraindication, or medically justifiable reason precludes statin use

* BMI**: Body Mass Index

† Adherence is defined as at least 80% of the prescribed dose.
the event the patient is unable to complete either of the high-intensity statin trials at the maximum approved dosing

- OR
- Patient has a documented contraindication (e.g., active liver disease, pregnancy, breastfeeding), or medically justifiable reason that precludes statin use (e.g. patients has experienced rhabdomyolysis CK elevations ≥ 10x ULN, or statin intolerance).
  - Statin intolerance shall be defined in accordance with the National Lipid Association definition:
    - Inability to tolerate at least two statins (one at any dose, one at lowest daily dose) due to objectionable symptoms or abnormal biomarkers temporally related to statin use, reversible upon statin discontinuation and reproducible by re-challenge while excluding other known determinants. Other known determinants include low body mass index (BMI), acute infection, untreated or undertreated hypothyroidism, severe renal or hepatic dysfunction, organ transplant, recent severe trauma, HIV infection, Vitamin D deficiency, history of creatine kinase elevation, history of preexisting or unexplained muscle or joint pain, high level of physical activity, illicit drug abuse, excess alcohol use. Each statin trial, both initial and re-challenge shall be at least two weeks duration.
      - One statin at lowest starting daily dose
        - Rosuvastatin 5mg
        - Atorvastatin 10mg
        - Simvastatin 10mg
        - Lovastatin 20mg
        - Pravastatin 40mg
        - Fluvastatin 40mg
        - Pitavastatin 2mg
      - One statin at any daily dose
    - Patient’s current triglyceride level is less than 400 mg/dL
    - Patient has tried and failed the plan’s preferred PCSK9 inhibitor, Repatha
    - Praluent will be added to statin therapy unless a contraindication, or medically justifiable reason precludes statin use

III. Repatha® (evolocumab) may be considered medically necessary for the treatment of heterozygous familial hypercholesterolemia when the following criteria are met:

- Patient is 18 years of age or older
- Patient has a definite diagnosis of FH, which is documented
  - An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation; OR
  - Definite FH per Simon-Broome Diagnostic Criteria or Dutch Lipid Network Criteria
- Patient is engaging in healthy lifestyle changes including a low-fat diet (saturated fat <7% of total calories) and exercise program (150 minutes or more of moderate to vigorous intensity physical activity per week, or engaging as medically appropriate) demonstrated by notable improvement in body mass index (BMI)*, or other clinical indicators of progress (e.g., improvements in fasting blood glucose, lipid profile, exercise tolerability), documented in the medical record
- Patient has been unable to achieve an LDL-C reduction of ≥ 50% despite adherence‡ to the combination of lifestyle changes and at least three months of lipid lowering therapy:
  - BOTH high-intensity statins (atorvastatin 80 mg and rosuvastatin 40 mg) in combination with ezetimibe, OR...
TWO moderate intensity statins (e.g. pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin 80 mg, pitavastatin 2-4 mg, simvastatin 20-40 mg) in combination with ezetimibe, only in the event the patient is unable to complete either of the high-intensity statin trials at the maximum approved dosing

• OR
• Patient has a documented contraindication (e.g., active liver disease, pregnancy, breastfeeding), or medically justifiable reason that precludes statin use (e.g. patients has experienced rhabdomyolysis, CK elevations ≥ 10x ULN, or statin intolerance).
  • Statin intolerance shall be defined in accordance with the National Lipid Association definition:
    • Inability to tolerate at least two statins (one at any dose, one at lowest daily dose) due to objectionable symptoms or abnormal biomarkers temporally related to statin use, reversible upon statin discontinuation and reproducible by re-challenge while excluding other known determinants. Other known determinants include low body mass index (BMI), acute infection, untreated or undertreated hypothyroidism, severe renal or hepatic dysfunction, organ transplant, recent severe trauma, HIV infection, Vitamin D deficiency, history of creatine kinase elevation, history of preexisting or unexplained muscle or joint pain, high level of physical activity, illicit drug abuse, excess alcohol use. Each statin trial, both initial and re-challenge shall be at least two weeks duration.
      o One statin at lowest starting daily dose
        • Rosuvastatin 5mg
        • Atorvastatin 10mg
        • Simvastatin 10mg
        • Lovastatin 20mg
        • Pravastatin 40mg
        • Fluvastatin 40mg
        • Pitavastatin 2mg
      o One statin at any daily dose

• Patient’s current triglyceride level is less than 400 mg/dL
• Repatha will be added to statin therapy unless a contraindication, or medically justifiable reason precludes statin use

IV. Praluent (alirocumab) may be considered medically necessary for the treatment of heterozygous familial hypercholesterolemia when the following criteria are met:

• Patient is 18 years of age or older
• Patient has a definite diagnosis of FH, which is documented
  o An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation; OR
  o Definite FH per Simon-Broome Diagnostic Criteria or Dutch Lipid Network Criteria
• Patient is engaging in healthy lifestyle changes including a low-fat diet (saturated fat <7% of total calories) and exercise program (150 minutes or more of moderate to vigorous intensity physical activity per week, or engaging as medically appropriate) demonstrated by notable improvement in body mass index (BMI)*, or other clinical indicators of progress (e.g., improvements in fasting blood glucose, lipid profile, exercise tolerability), documented in the medical record
• Patient has been unable to achieve an LDL-C reduction of ≥ 50% despite adherence† to the combination of lifestyle changes and at least three months of lipid lowering therapy:

*BMI
†Adherence
O. BOTH high-intensity statins (atorvastatin 80 mg and rosuvastatin 40 mg) in combination with ezetimibe, OR
O. TWO moderate intensity statins (e.g. pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin 80 mg, pitavastatin 2-4 mg, simvastatin 20-40 mg) in combination with ezetimibe, only in the event the patient is unable to complete either of the high-intensity statin trials at the maximum approved dosing

• OR
• Patient has a documented contraindication (e.g., active liver disease, pregnancy, breastfeeding), or medically justifiable reason that precludes statin use (e.g. patients has experienced rhabdomyolysis, CK elevations ≥ 10x ULN, or statin intolerance).
  ▪ Statin intolerance shall be defined in accordance with the National Lipid Association definition:
    • Inability to tolerate at least two statins (one at any dose, one at lowest daily dose) due to objectionable symptoms or abnormal biomarkers temporally related to statin use, reversible upon statin discontinuation and reproducible by re-challenge while excluding other known determinants. Other known determinants include low body mass index (BMI), acute infection, untreated or undertreated hypothyroidism, severe renal or hepatic dysfunction, organ transplant, recent severe trauma, HIV infection, Vitamin D deficiency, history of creatine kinase elevation, history of preexisting or unexplained muscle or joint pain, high level of physical activity, illicit drug abuse, excess alcohol use. Each statin trial, both initial and re-challenge shall be at least two weeks duration.
      o One statin at lowest starting daily dose
        ▪ Rosuvastatin 5mg
        ▪ Atorvastatin 10mg
        ▪ Simvastatin 10mg
        ▪ Lovastatin 20mg
        ▪ Pravastatin 40mg
        ▪ Fluvastatin 40mg
        ▪ Pitavastatin 2mg
      o One statin at any daily dose

• Patient’s current triglyceride level is less than 400 mg/dL
• Patient has tried and failed the plan’s preferred PCSK9 inhibitor, Repatha
• Praluent will be added to statin therapy unless a contraindication, or medically justifiable reason precludes statin use

V. Repatha (evolocumab) may be considered medically necessary for the treatment of homozygous familial hypercholesterolemia when the following criteria are met:
• Patient is 13 years of age or older
• Patient has a definite diagnosis of homozygous familial hypercholesterolemia (HoFH), which is documented:
  o Mutation in both alleles at LDL receptor, ApoB, PCSK9 or LDL receptor adaptor protein gene locus; OR
  o Untreated LDL-C > 500 mg/dL OR unknown untreated LDL-C with treated LDL-C > 300 mg/dL with one of the following:
    ▪ Tendon or cutaneous xanthomas at age 10 or younger
    ▪ Definite FH by Simon-Broome Diagnostic Criteria or Dutch Lipid Clinic Network Criteria in both parents
• Patient is engaging in healthy lifestyle changes including a low-fat diet (saturated fat <7% of total calories) and exercise program (150 minutes or more of moderate to vigorous intensity physical activity per week, or engaging as medically appropriate) demonstrated by notable improvement in body mass index (BMI)*, or other clinical indicators of progress (e.g., improvements in fasting blood glucose, lipid profile, exercise tolerability), documented in the medical record
• Patient’s current triglyceride level is less than 400 mg/dL
• Repatha will be added to maximally tolerated statin therapy unless a contraindication (e.g., active liver disease, pregnancy, breastfeeding), or medically justifiable reason precludes statin use (e.g., patients has experienced rhabdomyolysis, CK elevations ≥ 10x ULN, or statin intolerance).
  ▪ Statin intolerance shall be defined in accordance with the National Lipid Association definition:
    • Inability to tolerate at least two statins (one at any dose, one at lowest daily dose) due to objectionable symptoms or abnormal biomarkers temporally related to statin use, reversible upon statin discontinuation and reproducible by re-challenge while excluding other known determinants. Other known determinants include low body mass index (BMI), acute infection, untreated or undertreated hypothyroidism, severe renal or hepatic dysfunction, organ transplant, recent severe trauma, HIV infection, Vitamin D deficiency, history of creatine kinase elevation, history of preexisting or unexplained muscle or joint pain, high level of physical activity, illicit drug abuse, excess alcohol use. Each statin trial, both initial and re-challenge shall be at least two weeks duration.
      o One statin at lowest starting daily dose
        ▪ Rosuvastatin 5mg
        ▪ Atorvastatin 10mg
        ▪ Simvastatin 10mg
        ▪ Lovastatin 20mg
        ▪ Pravastatin 40mg
        ▪ Fluvastatin 40mg
        ▪ Pitavastatin 2mg
      o One statin at any daily dose
  • Repatha will not be combined with Praluent, Kynamro or Juxtapid

*If patient is within healthy BMI range, documentation must satisfy that he or she is engaging in low fat diet and exercise program

†Please note: Documentation of LDL-C levels are required (untreated baseline and current [within 30 days of prior authorization request]); pharmacy refill records may be requested to demonstrate adherence with medication

Initial approval will be for 3 months

Renewal (for either Repatha or Praluent) may be authorized for any patients who have had a documented LDL-C reduction of ≥ 35%, or an absolute reduction of ≥ 40 mg/dL, who have also demonstrated adherence with the PCSK9, statin therapy, and lifestyle modifications†.

Renewals will be approved for 12 months

†Please note: Documentation of LDL-C levels are required (untreated baseline and current [within 30 days of prior authorization request]); pharmacy refill records may be requested to demonstrate adherence with medication
The aforementioned drugs are considered **not medically necessary** for patients who do not meet the criteria set forth above.

**Quantity limits apply.** Praluent and Repatha* 2 pen/syringe per 28 days.

*Patients approved through the policy for the **homozygous** familial hypercholesterolemia (HoFH) indication can be approved Repatha for a quantity of 3 pens/syringes per 30 days.

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**CLINICAL RATIONALE**

Repatha (evolocumab) and Praluent (alirocumab) are both human monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9). PCSK9 is a regulatory protease that binds to low density lipoprotein receptors (LDL-R) in the liver, inducing their degradation, which limits the ability of hepatocytes to remove LDL-C from circulation. By inhibiting this process, the PCSK9 agents result in lower levels of circulating LDL-C. Praluent was approved by the FDA for the treatment of adult patients with clinical ASCVD and HeFH, as **adjunct to diet and maximally tolerated statin therapy**, for those who require additional lowering of LDL-C. In addition to these two indications, Repatha also carries an indication for the treatment of HoFH, as an adjunct to diet and other lipid lowering therapies (e.g. statin, ezetimibe, LDL apheresis), in patients at least 13 years of age.

Approximately one-third of American adults have ASCVD; it is the most common cause of death in the United States. Hypercholesterolemia, or elevation of LDL-C, is a major risk factor for ASCVD. Multiple randomized clinical trials have demonstrated that lowering LDL-C with statin therapy reduces the risk of MI, stroke, and death from ASCVD. Statins are the standard of treatment, demonstrating LDL-lowering capacity of 30-50% with moderate intensity therapy and greater than 50% with high intensity. Cardiovascular risk reduction is likely not only related to the statins ability to lower LDL-C, but also a result of their pleiotropic effects. Statins are the only cholesterol medication, to date, that have consistently demonstrated not only a beneficial effect on the lipid profile, but also an improvement in patient centered outcomes including reduction in MI, stroke and death related to cardiovascular causes. Cardiovascular risk is reduced by 20% with a 39 mg/dL reduction in LDL-C level as a result of statin therapy. Other non-statin drugs (e.g. hormone therapy, niacin, torcetrapib) have not demonstrated reduction in cardiovascular events in trials, despite their ability to lower LDL-C. Zetia (ezetimibe) is the only non-statin drug to have demonstrated its additional lowering of LDL-C, when combined with a statin, reduces the CV event rate. There were several limitations to the IMPROVE-IT trial, however, and while this reduction was statistically significant, its clinical relevance remains debated. Based on a marginal reduction in events by 6% (95% CI 1 to 11%), and an absolute risk reduction of only 2%, Zetia would need to be added to statin therapy to approximately 50 patients for over 5 years to prevent 1 event.

The 2013 American Heart Association/American College of Cardiology (AHA/ACC) guidelines emphasize the importance of statin therapy, and move away from the previous treat-to-target LDL goals, instead recommending appropriate statin intensity based on risk. These guidelines do not support the addition of other lipid-lowering treatment strategies, primarily as there is not evidence to support their use in cardiovascular risk reduction, nor is there a strong evidentiary base to suggest reducing LDL-C to a specific goal (<100, <70) improves outcomes.

Without question, both PCSK9 inhibitors have demonstrated they significantly reduce LDL-C, regardless of the background treatment or comparator. As would be anticipated, the percentage reduction in LDL-C is greater when PCSK9 inhibitors are compared to placebo (58.8%) than when compared to ezetimibe (36.2%). Whether this dramatic lowering of LDL-C translates into cardiovascular risk reduction or long-term safety concerns is unknown. No trials have been prospectively designed and powered to evaluate cardiovascular outcomes. While PCSK9 agents appear safe and well tolerated thus far, the vast majority
of studies have less than 6 months of follow-up. There has been a slight signal of increased neurocognitive
events noted in studies, but thus far, this is not statistically significant in comparison to control. In Praluent
trials, approximately 37% of Praluent treated patients had LDL-C less than 25 mg/dL. Theoretical concerns
exist with extremely low levels of cholesterol; the long-term effect of this largely unknown. Large long-term
studies, anticipated in 2017, are needed to ensure the LDL-C lowering demonstrated with PCSK9 inhibitors
translates into improved cardiovascular outcomes, and not safety concerns.

Statin intolerance can prevent patients with cardiovascular risk from receiving adequate therapy, yet there
has been some difficulty in establishing a unified definition and outlining appropriate management. A recent
article on statin intolerance in Circulation, stated the following, "Before considering the use of a second-line
alternative drug, patients should try statin rechallenge, alternative regimens, doses, or different types of
statins. In most cases, rechallenge with a statin after a brief period of drug discontinuation ("drug holiday")
can be successful". The article cited a study of 11,124 patients in whom statins were discontinued as a
result of adverse effects. When rechallenged, 92% were still taking a statin 12 months after the statin-
related event. Recently the European Atherosclerosis Society (EAS) provided expert consensus for the
assessment and management of statin-associated muscle symptoms, which focused on excluding other
potential causes or risk factors, withdrawal of the statin, followed by one or more rechallenges to
demonstrate causality, use of an alternative statin or intermittent dosing, wherever possible, in order to
continue statin medication for the cardiovascular benefit. Alternate day or twice-weekly dosing utilizing a
high intensity statin with a longer half-life (e.g. atorvastatin, rosuvastatin, and pitavastatin) is also
recommended, with ezetimibe, the “first-choice” non-statin “based on its safety profile, as well as recent
evidence of cardiovascular outcomes benefit in IMPROVE-IT”. A recent position paper by an International
Lipid Expert Panel, supported the EAS consensus recommendations, and further complemented it by
providing the following proposed definition for statin intolerance - 1) the inability to tolerate at least 2 different
statins – one statin at the lowest starting average daily dose at any dose, 2) intolerance associated with
confirmed, intolerable statin-related adverse effects(s) or significant biomarker abnormalities, 3) symptom
or biomarker changes resolution or significant improvement upon dose decrease or discontinuation, 4)
symptoms or biomarker changes not attributable to established predispositions such as drug-drug
interactions and recognized conditions increasing the risk of statin intolerance. The National Lipid
Association confirmed the previous organizations’ stances by defining statin intolerance as the inability to
tolerate at least two statins due to objectionable symptoms or abnormal biomarkers temporally related to
statin use, reversible upon statin discontinuation and reproducible by re-challenge while excluding other
known determinants. One statin, upon initial and re-challenge trials, shall be started at lowest daily dose
while the other may be started at any daily dose. Statin therapy is the essential drug therapy for
cardiovascular risk reduction; it should not be abandoned lightly.
PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD-CM diagnostic codes.

- Code(s), if applicable

REFERENCES

- Repatha [prescribing information]. Thousand Oaks, CA; Amgen, Inc.: August 2015.
- Praluent [prescribing information]. Bridgewater, NJ; Sanofi-aventis US, LLC.: July 2015
• Robinson JG, Colhoun HM, Bays HE, et al. Efficacy and safety of alirocumab as add-on therapy in high-cardiovascular-risk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20 mg): design and rationale of the ODYSSEY OPTIONS Studies. *Clin Cardiol*. 2014;37(10):597-604.

**POLICY HISTORY**

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