PCSK9 Inhibitors

NOTICE

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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.

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.

FDA-Approved Indications

Praluent

- To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease
- As 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
- As an adjunct to other LDL-C-lowering therapies in adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C

Repatha

- To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease
- As an 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
- As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C
- As an adjunct to diet and other LDL-lowering therapies in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH), to reduce LDL-C

Note: Repatha and Praluent are not approved or recommended for the primary prevention of cardiovascular events and for the lowering of low-density lipoprotein cholesterol in patients with primary hyperlipidemia who do not have HeFH or clinical ASCVD as the use of PCSK9 Inhibitors in this population is not supported by the 2018 American College of Cardiology/American Heart Association Cholesterol Clinical Practice Guidelines or current evidence.

POLICY

Prescriber Requirement

The medication must be prescribed by or in consultation with a cardiologist, endocrinologist, lipid specialist, or cardiometabolic specialist.

Must meet BOTH the Preferred Drug Plan Design and Criteria for Initial Approval/Continuation of Therapy when both are applicable.

Preferred Drug Plan Design

A. Criteria for initial approval and Continuation of Therapy will only apply for Praluent (alirocumab) when at least ONE of the following criteria are met:
    a) The patient has had an inadequate response to treatment, intolerable adverse event, or has a contraindication to therapy with the plan's preferred PCSK9 inhibitor, Repatha

Criteria for Initial Approval

A. **Repatha** (evolocumab) and **Praluent** (alirocumab) may be considered **medically necessary** for the treatment of **clinical atherosclerotic cardiovascular disease ASCVD** (Appendix A)* when all of the following criteria are met:
1. Patient is 18 years of age or older
2. Patient has a history of clinical ASCVD (Appendix A)
3. Patient is engaging in healthy lifestyle changes
4. Patient has been unable to achieve an LDL-C < 70 mg/dL despite adherence† to the combination of lifestyle changes and at least three months of the following lipid lowering therapy:
    a). A trial of BOTH high-intensity statins (atorvastatin 40-80 mg and rosuvastatin 20-40 mg) at a maximum tolerated dose in combination with ezetimibe, **OR**
    b). A trial of 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
5. Patient will continue other traditional low-density lipoprotein-cholesterol (LDL-C) lowering therapies (e.g., maximally tolerated statins, ezetimibe) in combination with the requested medication
6. The requested medication will not be combined with other PCSK9-targeted therapy (e.g., Praluent, Repatha, Leqvio)

OR

1. Patient is 18 years of age or older
2. Patient has a history of clinical ASCVD (Appendix A)
3. Patient is engaging in healthy lifestyle changes
4. The requested medication will not be combined with other PCSK9-targeted therapy (e.g., Praluent, Repatha, Leqvio)
5. Patient has a current LDL-C level ≥ 70 mg/dL

6. 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).
    a). Statin intolerance shall be defined in accordance with the National Lipid Association definition:
        i. 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.
            - A trial of 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

B. **Repatha** (evolocumab) and **Praluent** (alirocumab) may be considered **medically necessary** for the treatment of **heterozygous familial hypercholesterolemia** when the following criteria are met:
1. Patient is 10 years of age or older if the requested drug is Repatha or 18 years of age or older if the requested drug is Praluent
2. Patient has a diagnosis of HeFH, which is documented and confirmed by ONE of the following:
    a). An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation; **OR**
    b). Definite or possible FH per Simon-Broome Diagnostic Criteria (Appendix B); **OR**
    c). Dutch Lipid Network Criteria greater than 5 (Appendix C)
3. Patient is engaging in healthy lifestyle changes
4. Patient has been unable to achieve an LDL-C reduction of < 100 mg/dL (or ≤ 70 mg/dL with clinical atherosclerotic cardiovascular disease [ASCVD]) despite adherence† to the combination of lifestyle changes and at least three months of the following lipid lowering therapy:
    a). A trial of BOTH high-intensity statins (atorvastatin 40-80 mg and rosuvastatin 20-40 mg) at a maximum tolerated dose in combination with ezetimibe, OR
    b). A trial of 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
5. The requested medication will not be combined with other PCSK9-targeted therapy (e.g., Praluent, Repatha, Leqvio)
6. Patient will continue other traditional low-density lipoprotein-cholesterol (LDL-C) lowering therapies (e.g., maximally tolerated statins, ezetimibe) in combination with the requested medication

OR

1. Patient is 10 years of age or older if the requested drug is Repatha or 18 years of age or older if the requested drug is Praluent
2. Patient has a diagnosis of HeFH, which is documented and confirmed by ONE of the following:
   a). An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation; **OR**
   b). Definite or possible FH per Simon-Broome Diagnostic Criteria (Appendix B); **OR**
   c). Dutch Lipid Network Criteria score greater than 5 (Appendix C)
3. Patient is engaging in healthy lifestyle changes
4. Patient has a current LDL-C level ≥ 100 mg/dL (or level ≥ 70 mg/dL with clinical atherosclerotic cardiovascular disease [ASCVD])
5. 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).
   a). Statin intolerance shall be defined in accordance with the National Lipid Association definition:
      i. 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.
         - A trial of 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
6. The requested medication will not be combined with other PCSK9-targeted therapy (e.g., Praluent, Repatha, Leqvio)

C. **Repatha** (evolocumab) and **Praluent** (alirocumab) may be considered **medically necessary** for the treatment of **homozygous familial hypercholesterolemia** when the following criteria are met:
1. Patient is 10 years of age or older if the requested drug is Repatha or 18 years of age or older if the requested drug is Praluent
2. Patient has a definite diagnosis of homozygous familial hypercholesterolemia (HoFH), which is documented and confirmed by ONE of the following:
   a). Mutation in both alleles at LDL receptor, ApoB, PCSK9 or LDL receptor adaptor protein 1/ARH adaptor protein 1 gene locus; **OR**
   b). Untreated LDL-C > 500 mg/dL OR unknown untreated LDL-C with treated LDL-C > 300 mg/dL plus one of the following:
      i. Tendon or cutaneous xanthomas before age 10
      ii. Definite FH by Simon-Broome Diagnostic Criteria or Dutch Lipid Clinic Network Criteria in both parents (Appendix B and C)
3. Patient has been unable to achieve an LDL-C reduction of ≥ 50% despite adherence† to at least three months of the following lipid lowering therapy:

a). A trial of ONE high-intensity statin (atorvastatin 40-80 mg or rosuvastatin 20-40 mg) at a maximum tolerated dose in combination with ezetimibe or the patient is unable to reach the high intensity dose due to intolerability.

4. The requested medication will not be combined with other PCSK9-targeted therapy (e.g., Praluent, Repatha, Leqvio) or Juxtapid
5. Patient will continue other traditional low-density lipoprotein-cholesterol (LDL-C) lowering therapies (e.g., maximally tolerated statins, ezetimibe) in combination with the requested medication

OR

1. Patient is 10 years of age or older if the requested drug is Repatha or 18 years of age or older if the requested drug is Praluent
2. Patient has a definite diagnosis of homozygous familial hypercholesterolemia (HoFH), which is documented and confirmed by ONE of the following:
   a). Mutation in both alleles at LDL receptor, ApoB, PCSK9 or LDL receptor adaptor protein 1/ARH adaptor protein 1 gene locus; **OR**
   b). Untreated LDL-C > 500 mg/dL OR unknown untreated LDL-C with treated LDL-C > 300 mg/dL plus one of the following:
      i. Tendon or cutaneous xanthomas at age 10 or younger
      ii. Definite FH by Simon-Broome Diagnostic Criteria or Dutch Lipid Clinic Network Criteria in both parents (Appendix B and C)
3. Patient has a documented contraindication (e.g., active liver disease, pregnancy, breastfeeding), or a medically justifiable reason that precludes statin use (e.g., patient has experienced rhabdomyolysis, CK elevations ≥ 10x ULN, or statin intolerance).
   a). Statin intolerance shall be defined in accordance with the National Lipid Association definition:
      ii. 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.
         - A trial of 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
4. The requested medication will not be combined with other PCSK9-targeted therapy (e.g., Praluent, Repatha, Leqvio) or Juxtapid

†Please note: Documentation of LDL-C levels are required (untreated baseline and current [within 60 days of prior authorization request]); pharmacy refill records may be requested to demonstrate adherence with medication

Initial approval will be for **6 months**

Continuation of Therapy

The continuation of therapy for either Repatha (evolocumab) or Praluent (alirocumab) may be considered **medically necessary** for any patient who meets the following criteria:

- Must have a documented positive clinical response to therapy as defined by achieving or maintaining an LDL-C reduction (i.e., LDL is now at goal or significant reduction in LDL-C levels from baseline)†; **AND**
- Patient continues treatment with other traditional LDL-C lowering therapies (e.g., maximally tolerated statins, ezetimibe) in combination with the requested medication with demonstrated adherence† if no contraindication or intolerance
- Patient continues to engage in healthy lifestyle changes
- The requested medication will not be combined with other PCSK9-targeted therapy (e.g., Repatha, Praluent, Leqvio) or Juxtapid

Renewals will be approved for **12 months**

†Please note: Documentation of LDL-C levels are required (untreated baseline and current [within 90 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.

Dosage and Administration

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

Quantity Limits Apply

- Praluent and Repatha‡ 2 pens/syringes per 28 days.
- Repatha‡ 1 Pushtronex system/2 autoinjectors 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 or autoinjectors per 30 days.

APPENDIX

APPENDIX A: Clinical Atherosclerotic Cardiovascular Disease (ASCVD)

- Acute coronary syndromes
- Myocardial infarction
- Stable or unstable angina
- Coronary or other arterial revascularization procedure (e.g., percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery)
- Stroke of presumed atherosclerotic origin
- Transient ischemic attack (TIA)
- Non-cardiac peripheral arterial disease (PAD) of presumed atherosclerotic origin (e.g., carotid artery stenosis, lower extremity PAD)
- Obstructive coronary artery disease (defined as fifty percent or greater stenosis on cardiac computed tomography angiogram or catheterization)
  Coronary Artery Calcium (CAC) Score ≥ 1000

APPENDIX B: Simon Broome Register diagnostic criteria for Heterozygous Familial Hypercholesterolemia

Definite familial hypercholesterolemia:

- Total cholesterol > 290 mg/dL or LDL-C > 190 mg/dL in patients over 16 years of age or total cholesterol > 260 mg/dL or LDL-C > 155 mg/dL in patients less than 16 years of age
  AND
  Tendon xanthomas in the patient, first (parent, sibling or child) or second degree relative (grandparent, uncle or aunt); OR presence LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Possible familial hypercholesterolemia:

- Total cholesterol > 290 mg/dL or LDL-C > 190 mg/dL in patients over 16 years of age or total cholesterol > 260 mg/dL or LDL-C > 155 mg/dL in patients less than 16 years of age
  AND
- Family history of at least one of the following:
  - Family history of myocardial infarction at age 60 years or younger in first degree relative or age 50 years or younger in second-degree relative
    OR
  - Family history of elevated total cholesterol of greater than 290 mg/dL in adult first- or second-degree relative or total cholesterol greater than 260 mg/dL in child, brother or sister aged younger than 16 years

APPENDIX C: Dutch Lipid Clinic Network diagnostic criteria for Familial Hypercholesterolemia

Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia			
Family History			
First degree relative with known premature (men < 55 yrs, women < 60 yrs) coronary vascular disease			1
First degree relative with known LDL-cholesterol >95th percentile for age and sex			
and/or			
First degree relative with tendon xanthomata and/or arcus cornealis			2
Children below 18 yrs with LDL-cholesterol >95th percentile for age and sex			
Clinical History			
Patient has premature (men < 55 yrs, women < 60 yrs) coronary artery disease			2
Patient has premature (men < 55 yrs, women < 60 yrs) cerebral or peripheral vascular disease			1
Physical Examination			
Tendon xanthomata			6
Arcus cornealis below the age of 45 yrs			4
Laboratory Analysis			
	mmol/L	mg/dL	
LDL-cholesterol	> 8.5	> 330	8
LDL-cholesterol	6.5 – 8.4	250 – 329	5
LDL-cholesterol	5.0 – 6.4	190 – 249	3
LDL-cholesterol	4.0 – 4.9	155 – 189	1
(HDL-cholesterol and triglycerides are normal)			
DNA Analysis			
Functional mutation low-density lipoprotein receptor gene present			6
Diagnosis of HeFH is:			
Certain When		> 8 points	
Probable When		6-8 points	
Possible When		3-5 points	

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.

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) has been found to reduce the rate of CV events when used in combination with a statin. 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 moved away from the previous treat-to-target LDL goals, instead of 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. A 2017 update to the 2016 American College of Cardiology expert consensus decision pathway (ECDP) provided guidance for consideration of adding non-statin therapy. The defined thresholds for ASCVD risk-reduction are ≥50% reduction in LDL-C. The update also considered a target of LDL-C <70 mg/dL or non-HDL-C <100 mg/dL for all patients with clinical ASCVD and baseline LDL-C of 70-189 mg/dL appropriate as well. The 2018 American Heart Association/American College of Cardiology (AHA/ACC) guidelines continue to emphasize the importance of statin therapy and reestablishes LDL goals, incorporates new evidence on nonstatin therapies, and addresses concerns about ASCVD risk overestimation for primary prevention. Although 50% LDL cholesterol lowering is still the goal for patients treated with a high-intensity statin, an LDL goal of less than 70 mg/dL warrants consideration of ezetimibe followed by PCSK9 inhibitors in patients who have not reached their target LDL. Populations benefited by statins remain relatively unchanged, except that PCSK9 inhibitors are recommended for secondary prevention with a maximally tolerated statin in very high-risk ASCVD patients (defined as a history of multiple cardiovascular events or one major event and multiple high-risk conditions).

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%). While PCSK9 agents appear safe and well tolerated thus far, the long-term safety (>3 years) is uncertain. 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.

The FOURIER trial evaluated the addition of Repatha (evolocumab) to statin therapy. Addition of this PCSK9 inhibitor to statin therapy significantly reduced CV events and the magnitude of risk reduction was seen to increase after the first year. Risk reduction in the first year was 12%, but increased to 19% in subsequent years. This trial also demonstrated beneficial CV outcomes when LDL-C was treated well below targets. The median LDL-C for treatment participants was 30 mg/dL. Evolocumab would need to be added to statin therapy for approximately 67 patients over 2 years to prevent 1 event from occurring.

The ODYSSEY OUTCOMES trial results were presented at the 67th Scientific Session of the American College of Cardiology (ACC) meeting on March 10, 2018. This trial was a multi-site randomized trial that tested Praluent (alirocumab) versus placebo in nearly 19,000 patients who experienced an ACS event between 1-12 months (median 2.6 months) before enrolling in the trial and were receiving a maximally-tolerated statin. The primary outcome was composite of cardiovascular death, MI, stroke, and hospitalization for unstable angina (MACE). Compared to placebo, Praluent reduced the overall risk of the primary efficacy outcome with a hazard ratio (HR) of 0.85 among all patients. The HR for all-cause mortality was also 0.85, and for CV mortality was 0.88 (although not statistically significant). Patients with ACS and baseline LDL-C levels ≥100mg/dL experienced a more pronounced effect from Praluent, reducing their risk of MACE by 24% (HR 0.76, ARR 3.4%), Praluent was also associated with a lower risk of death from any cause by 29% (HR 0.71, ARR 7.7%) in patients with LDL-C levels ≥100mg/dL.

It's difficult to ascertain whether this benefit is a class effect or drug-specific due to differences in the study design between the ODYSSEY OUTCOMES and FOURIER trials. Key differences include the number of study participants, with 27,564 in the FOURIER trial, compared to 18,924 in the ODYSSEY OUTCOMES trial. The median duration of follow-up in the FOURIER trial was 2.2 years, while the duration of the ODYSSEY OUTCOMES trial was 4 years. The FOURIER trial did not find any differences in risk reduction in regard to baseline LDL-C, compared to the ODYSSEY OUTCOMES trial in which those patients with a higher baseline LDL-C recognized the greatest benefit.

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

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POLICY HISTORY

Policy #: 05.01.90
Policy Creation: November 2015
Reviewed: October 2022
Revised: October 2022
Current Effective Date: January 1, 2023