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DRUG POLICY

PCSK9 Inhibitors

NOTICE

This policy contains information which is clinical in nature. The policy is not medical advice. The information in this policy is used by Wellmark to make determinations whether medical treatment is covered under the terms of a Wellmark member's health benefit plan. Physicians and other health care providers are responsible for medical advice and treatment. If you have specific health care needs, you should consult an appropriate health care professional. If you would like to request an accessible version of this document, please contact customer service at 800-524-9242.

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. 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).

Repatha and Praluent are not covered 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.

POLICY

Required Documentation

The following information is necessary to initiate the prior authorization review:

- Untreated baseline LDL level, LDL levels while receiving statin therapy (prior to starting PCSK9 therapy) and current LDL levels on PCSK9 inhibitor (if applicable)
- BMI

- Historic BMI results showing a notable improvement or chart notes demonstrating an improvement in other clinical factors as a result of the lifestyle changes
- Transaminase levels (if applicable)
- Chart notes demonstrating statin intolerance or contraindication to statin therapy (if applicable)
- Lab results (i.e. LDL-receptor mutation, familial defective apo B-100, or PCSK9 gain-of-function mutation) or rating scale (i.e. Simon-Broome Diagnostic Criteria or Dutch Lipid Network Criteria) demonstrating heterozygous familial hypercholesterolemia diagnosis (if applicable)

Criteria for Initial Approval

A. Repatha® (evolocumab) 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 is engaging in healthy lifestyle changes including a healthy-fat diet (saturated fat <10% of total calories) emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish 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
3. Patient is considered high risk (Appendix B) and has been unable to achieve an LDL-C < 70 mg/dL or a non-HDL-C level of < 100 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
4. Repatha will be added to statin therapy

OR

1. Patient is 18 years of age or older
2. Patient is engaging in healthy lifestyle changes including a healthy-fat diet (saturated fat <10% of total calories) emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish 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
3. 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. Praluent (alirocumab) may be considered medically necessary for the treatment of clinical atherosclerotic cardiovascular disease ASCVD (Appendix A) when the following criteria are met:

1. Patient is 18 years of age or older
2. Patient is engaging in healthy lifestyle changes including a healthy-fat diet (saturated fat <10% of total calories) emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish 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
3. Patient is considered high risk (Appendix B) and has been unable to achieve an LDL-C < 70 mg/dL or a non-HDL-C level of < 100 mg/dL despite adherence[†] to the combination of lifestyle changes and at least three months of the following lipid lowering therapy:
 - c). 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**
 - d). 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
4. Patient has tried and failed the plan's preferred PCSK9 inhibitor, Repatha
5. Praluent will be added to statin therapy

OR

1. Patient is 18 years of age or older
2. Patient is engaging in healthy lifestyle changes including a healthy-fat diet (saturated fat <10% of total calories) emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish 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
3. 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 $\geq 10x$ 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. Patient has tried and failed the plan's preferred PCSK9 inhibitor, Repatha

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

1. Patient is 18 years of age or older
2. Patient has a definite diagnosis of HeFH, which is documented
 - a). An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation; **OR**
 - b). Definite FH per Simon-Broome Diagnostic Criteria or Dutch Lipid Network Criteria
3. Patient is engaging in healthy lifestyle changes including a healthy-fat diet (saturated fat <10% of total calories) emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish 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
4. Patient has been unable to achieve an LDL-C reduction of $\geq 50\%$ or LDL-C < 100 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. Repatha will be added to statin therapy

OR

1. Patient is 18 years of age or older
2. Patient has a definite diagnosis of HeFH, which is documented
 - a). An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation; **OR**
 - b). Definite FH per Simon-Broome Diagnostic Criteria or Dutch Lipid Network Criteria

3. Patient is engaging in healthy lifestyle changes including a healthy-fat diet (saturated fat <10% of total calories) emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish 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
4. 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 $\geq 10x$ 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.
 - o A trial of 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

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

1. Patient is 18 years of age or older
2. Patient has a definite diagnosis of HeFH, which is documented
 - a). An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation; **OR**
 - b). Definite FH per Simon-Broome Diagnostic Criteria or Dutch Lipid Network Criteria
3. Patient is engaging in healthy lifestyle changes including a healthy-fat diet (saturated fat <10% of total calories) emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish 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
4. Patient has been unable to achieve an LDL-C reduction of $\geq 50\%$ or LDL-C < 100 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 has tried and failed the plan's preferred PCSK9 inhibitor, Repatha
6. Praluent will be added to statin therapy

OR

1. Patient is 18 years of age or older
2. Patient has a definite diagnosis of HeFH, which is documented
 - a). An LDL-receptor mutation, familial defective apo B-100, or a PCSK9 gain-of-function mutation; **OR**
 - b). Definite FH per Simon-Broome Diagnostic Criteria or Dutch Lipid Network Criteria
3. Patient is engaging in healthy lifestyle changes including a healthy-fat diet (saturated fat <10% of total calories) emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish 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
4. 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 $\geq 10x$ 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.
 - o A trial of 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
5. Patient has tried and failed the plan's preferred PCSK9 inhibitor, Repatha

E. Repatha (evolocumab) may be considered **medically necessary** for the treatment of **homozygous familial hypercholesterolemia** when the following criteria are met:

1. Patient is 13 years of age or older
2. Patient has a definite diagnosis of homozygous familial hypercholesterolemia (HoFH), which is documented:
 - a). Mutation in both alleles at LDL receptor, ApoB, PCSK9 or LDL receptor adaptor protein gene locus; **OR**

- b). Untreated LDL-C > 500 mg/dL OR unknown untreated LDL-C with treated LDL-C > 300 mg/dL with 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
- 3. Patient has been unable to achieve an LDL-C reduction of $\geq 50\%$ 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. Repatha will not be combined with Praluent, Kynamro or Juxtapid
- 5. Repatha will be added to maximally tolerated statin therapy

OR

- 1. Patient is 13 years of age or older
- 2. Patient has a definite diagnosis of homozygous familial hypercholesterolemia (HoFH), which is documented:
 - a). Mutation in both alleles at LDL receptor, ApoB, PCSK9 or LDL receptor adaptor protein gene locus; **OR**
 - b). Untreated LDL-C > 500 mg/dL OR unknown untreated LDL-C with treated LDL-C > 300 mg/dL with 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
- 3. Patient has a documented contraindication (e.g., active liver disease, pregnancy, breastfeeding), or a medically justifiable reason that precludes statin use (e.g. patients has experienced rhabdomyolysis, CK elevations $\geq 10x$ ULN, or statin intolerance).
 - a). Statin intolerance shall be defined in accordance with the National Lipid Association definition:
 - iii. 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 A trial of 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
- 4. 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 healthy-fat diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish 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

Continuation of Therapy

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

- Must have a documented LDL-C reduction of $\geq 35\%$ or an absolute reduction of ≥ 40 mg/dL; **AND**
- Must have 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 pens/syringes 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.

APPENDIX

APPENDIX A: Clinical Atherosclerotic Cardiovascular Disease (ASCVD)

Clinical atherosclerotic cardiovascular disease (ASCVD) includes acute coronary syndrome (ACS), those with history of myocardial infarction (MI), stable or unstable angina or coronary or other arterial revascularization, stroke, transient ischemic attack (TIA), or peripheral arterial disease (PAD) including aortic aneurysm, all of atherosclerotic origin.

APPENDIX B: Very High-Risk* of Future ASCVD Events

*Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions

Major ASCVD Events
Recent ACS (within the past 12 mo)
History of MI (other than recent ACS event listed above)

History of ischemic stroke
Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)
High-Risk Conditions
Age ≥65 y
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major
ASCVD event(s)
Diabetes mellitus
Hypertension
Chronic Kidney Disease (eGFR 15-59 mL/min/1.73 m ²)
Current smoking
Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
History of congestive HF

ABI indicates ankle-brachial index; ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure; LDL, low-density lipoprotein cholesterol; and MI, myocardial infarction.

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) 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 (ECCP) provided guidance for consideration of adding non-statin therapy. The defined thresholds for ASCVD risk-reduction are $\geq 50\%$ 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 ≥ 100 mg/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 ≥ 100 mg/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 regards 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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