

Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors Alirocumab (PRALUENT®) / Evolocumab (REPATHA®)

Criteria for Use

January 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.

The Product Information should be consulted for detailed prescribing information.

See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or <http://vawww.pbm.va.gov> for further information.

Exclusion Criteria *If the answer to ANY item below is met, the patient should NOT receive alirocumab or evolocumab*

Contraindications:

- History of a serious hypersensitivity reaction to alirocumab or evolocumab
- Patient is pregnant
- Patient is lactating

Inclusion Criteria

- Patient is receiving care from a VA Cardiologist, Lipid Specialist, Endocrinologist or locally designated VA expert.**

AND

- Patient has a clinical or laboratory diagnosis of heterozygous familial hypercholesterolemia (HeFH).¹⁻³**

- Confirmed by genetic testing (low density lipoprotein receptor [LDL-R] DNA Sequencing Test or APOB [hypercholesterolemia] Mutation Analysis).**

OR

- Untreated LDL >220 mg/dL (ages 20-29) or >250 mg/dL (ages ≥30) AND**

- Family history of premature atherosclerotic cardiovascular disease (ASCVD)* **OR**
- Presence of tendon xanthomas at any age, arcus cornea in patients <45 years or tuberous xanthomas or xanthelasma in patients < 20 years of age.

AND

- A high dose statin (maximally dosed atorvastatin 80 mg or rosuvastatin 40 mg) plus ezetimibe has not resulted in at least a 50% reduction in LDL from untreated baseline despite confirmed adherence to treatment. (See "Issues for Consideration" for those HeFH patients with a documented intolerance to statins)**

AND

- Patient has been educated to follow a lipid-lowering diet and has been counseled to adopt healthy lifestyle changes to reduce cardiovascular risk including tobacco cessation, maintaining a healthy weight and optimizing physical activity.**

OR

- Patient has a clinical or laboratory diagnosis of homozygous familial hypercholesterolemia (HoFH):+**
 - Confirmed with genetic testing (mutation in LDL receptor: true homozygote or double heterozygote),**
 - OR**
 - Untreated LDL of >500 mg/dL**
 - OR**
 - Receiving maximally tolerated, clinically indicated lipid-lowering therapy (e.g., statins, ezetimibe) and LDL remains >300 mg/dL (adherence is confirmed), AND**
 - Physical findings including: tendon xanthomas at any age, arcus corneae in patients <45 years or tuberous xanthomas or xanthelasma in patients <20 years.

AND

- Patient has been educated to follow a lipid-lowering diet and has been counseled to adopt healthy lifestyle changes to reduce cardiovascular risk including tobacco cessation, maintaining a healthy weight and optimizing physical activity.**

**Family history of premature ASCVD: Onset in men <55 years and women <65 years, in first-degree relative. ASCVD: acute coronary syndrome, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, stable coronary heart disease, cerebrovascular accident or transient ischemic attack or atherosclerotic peripheral vascular disease.*

+See Issues for Consideration for discussion of PCSK9 inhibitors in HoFH

Dosage and Administration (See manufacturers prescribing information for more detailed information)**ALIROCUMAB:**

- The recommended initial dose of alirocumab is 75 mg administered subcutaneously every two weeks. If the LDL response is considered to be inadequate, the dose can be increased to a maximum of 150 mg given every two weeks.
- For missed doses, inform patients to administer the dose within seven days of the missed dose and then resume the original schedule. If the missed dose is not given within 7 days, skip the injection and resume the original schedule.
- Patients need to be educated on the proper technique for preparation and administration of alirocumab.
- Before administration, alirocumab must be allowed to come to room temperature for 30-40 minutes and should be administered as soon as possible after it has sufficiently warmed to room temperature. Up to three excursions (in and out of the refrigerator) are acceptable within the 24-hour period. It must not be kept out of the refrigerator for longer than 24 hours.
- Alirocumab is administered as a subcutaneous injection into the thigh, abdomen or upper arm using a single-dose of the prefilled pen or syringe. The site of injection should be rotated with every dose.
- Patients should be instructed NOT to shake alirocumab.
- Avoid injecting into areas of active skin disease or injury (e.g., sunburns, skin rashes or skin infection or inflammation).
- Alirocumab should not be administered with other injectable drugs at the same site of injection.
- Inform patients and caregivers to seek immediate medical attention if signs and symptoms of an allergic reaction occur.
- Pre-filled pens and pre-filled syringes should not be reused. The used pens and syringes should be disposed of in a puncture-resistant container. The container must not be recycled.

EVOLOCUMAB:

- In patients with HeFH or in those patients with established ASCVD (who require additional LDL lowering), the dose of evolocumab is 140 mg administered subcutaneously every 2 weeks or 420 mg once every month.
- If the dosing schedule is changed from every 2 weeks to once a month, or vice versa, the initial dose of the new regimen should be administered on the next scheduled date of the prior dosing regimen.
- If the 420 mg dose is prescribed, 3 evolocumab injections (140 mg each) must be administered subcutaneously within a 30-minute period. Alternatively, the FDA has approved a “hands free infusor device” (called the Pushtronex system) which adheres to the skin and infuses the 420 mg monthly dose in a single injection (prefilled cartridge).
- In patients with HoFH, the dose of evolocumab is 420 mg administered subcutaneously once a month. Since response to evolocumab is dependent upon the presence of functional LDL receptors, LDL should be measured within 4 to 8 weeks of the initiation of therapy to assess response.
- If a dose of evolocumab is missed, the patient should be instructed to administer the missed dose as soon as possible if there

are more than 7 days prior to their next dose OR omit the missed dose and resume dosing according to the original schedule.

- Patients and/or caregivers must be educated on the proper technique for preparation and administration of evolocumab.
- Evolocumab should be stored in the refrigerator and allowed to come to room temperature for at least 30 minutes prior to administration. Evolocumab can be stored at room temperature in its original packaging. However if stored outside of the refrigerator, it must be used within 30 days.
- Evolocumab is administered as a subcutaneous injection into the thigh, abdomen or upper arm. The injection should not be given into areas that are tender, bruised, red or indurated. The site of injection should be rotated with each injection.
- Other injectable drugs should not be administered at the same site as evolocumab.

Monitoring

- To assess response to alirocumab or evolocumab, LDL should be measured within 4-8 weeks of treatment initiation and after dose titration.
- To ensure prolonged LDL reduction with alirocumab or evolocumab, LDL should be checked periodically (e.g., every 6 months)
 - To confirm adherence to treatment with alirocumab or evolocumab and other lipid-lowering treatments.
 - To confirm continued response to therapy. The presence of anti-drug antibodies or neutralizing antibodies has been observed in clinical trials and some patients have experienced loss of efficacy and an increased incidence of adverse events. However, the clinical significance of these antibodies has not been fully elucidated.

Issues for Consideration

FDA APPROVED INDICATIONS/PLACE IN THERAPY:

- Alirocumab is FDA approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional LDL lowering.
- Evolocumab was approved by the FDA as an adjunct to diet and:
 - 1) Maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
 - 2) Other LDL lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional LDL lowering.
- Molecular genetic testing should be reserved for those patients in whom a clinical diagnosis cannot be made (i.e., according to published criteria) but whose serum lipids or clinical profile is suggestive of Familial Hypercholesterolemia.⁴⁻⁶ The patient should be referred for (or offered) genetic consultation PRIOR to genetic testing.
- A prompt reconsideration of all lipid-lowering treatments is recommended for all patients initiated on and tolerating treatment with alirocumab or evolocumab (e.g., possible discontinuation of BAS, switch to generic high potency statin if not already receiving [e.g., atorvastatin], etc.).
- Alirocumab or evolocumab are not recommended in patients with New York Heart Association III-IV congestive heart failure or those patients on dialysis since clinical evidence is lacking in these patients with any lipid-lowering agent.

Because of the inadequate clinical outcome and limited long-term safety data with alirocumab or evolocumab, use of these agents should be limited to the following groups:

- **Patients with a diagnosis of HeFH who have not achieved at least a 50% reduction in LDL from untreated baseline despite treatment with and confirmed adherence to maximum dose statins in addition to one other lipid-lowering therapy (e.g., ezetimibe).**
- **Patients with a diagnosis of HoFH on maximum lipid lowering therapy (e.g., statins, ezetimibe, LDL apheresis) and who require additional LDL lowering.**
 - There are no clinical trials evaluating alirocumab in patients with homozygous familial hypercholesterolemia (HoFH). However, there is some preliminary in-vitro evidence that alirocumab may also reduce LDL in this population of high risk patients with receptor defective HoFH.⁴
 - There are 2 completed trials evaluating the efficacy and safety of evolocumab in patients with HoFH. The LDL lowering response in these patients was less than that observed in patients with HeFH or those at high CV risk (approximately 23% vs. 50+%, respectively) in indirect studies. Patients who are LDL receptor

negative had no response to evolocumab.⁵⁻⁶

CLINICAL OUTCOMES AND SAFETY:

- **The effect of alirocumab on cardiovascular (CV) morbidity or mortality is unknown. The ODYSSEY OUTCOMES trial is underway which will enroll 18,000 having an ACS within the past year. The trial will be completed in late 2017.**
- **The effect of evolocumab on CV morbidity or mortality is unknown. The FOURIER Outcomes trial is ongoing and will examine the effect of evolocumab added to statins on clinical outcomes in 27,500 patients with established CV disease. Study completion is expected in late 2017 or early 2018.**
- Evidence to support treatment to a specific LDL target for reducing CV outcomes is lacking in most populations, including those with HeFH. Therefore, the LDL value that will result in the greatest reduction in CV risk is unknown.
- Both alirocumab and evolocumab have been associated with severe hypersensitivity reactions, patients and caregivers should be informed to seek immediate medical attention if signs and symptoms of an allergic reaction occur.
- Because of the relatively limited safety database (n=3340 exposed to alirocumab; n=5710 exposed to evolocumab) and the lack of long-term safety data for alirocumab or evolocumab, the FDA has required large, long-term, randomized controlled trials to assess the incidence and severity of adverse events associated with these agents including new-onset diabetes, injection site reactions, hypersensitivity reactions, immunogenicity and its consequences and neurologic events.

STATIN INTOLERANCE:

- Patients with a documented intolerance to statins:
 - Alirocumab and evolocumab were specifically not approved for use in the “statin intolerant” patient population because the FDA and its advisory committee were concerned that providers and patients may “bypass” statin therapy or use less intense regimens in favor of using PCSK9 inhibitors. Statins have the most evidence supporting improved cardiovascular outcomes, including all-cause mortality, and should remain first-line; while the PCSK9 inhibitors (despite lowering LDL) do not have evidence to support improved outcomes and only have limited safety data at this time.⁷
 - In a study of 341 patients (non-HeFH) with a documented intolerance to statins, nearly 75% of patients (63 pts were randomized to atorvastatin) were able to tolerate blinded atorvastatin 20 mg daily. In this study, statin intolerance was defined as: The inability to tolerate at least 2 different statins due to unexplained skeletal muscle-related complaints including pain or ache, weakness or muscle cramping that starts or worsens during treatment with statins and resolves when the statin is stopped. One of the two statins causing muscle complaints was required to have been administered at the lowest approved dose.⁸
 - In a study of 307 patients with self-reported statin intolerance who were randomized to evolocumab or ezetimibe, 8-13% of patients withdrew due to adverse events. Eighteen percent of patients were on at least a low statin dose throughout the study. None of the patients was re-challenged with statins prior to randomization to determine true intolerance and the study lasted only 12 weeks.⁹
 - In very high risk patients with HeFH or HoFH and documented statin intolerance, consider re-challenging them with at least a low to moderate dose statin. Alternate-day statin dosing reduces LDL but there is a lack of evidence that this dosing strategy reduces ASCVD events. However when possible, statins should remain as first-line therapy in primary and secondary prevention and use of alternate-day statins may be considered in patients unable to tolerate daily statins.
 - In HeFH patients with established ASCVD and with a documented intolerance to statins (defined as: a *trial of at least 3 statins which resulted in unexplained skeletal muscle-related complaints including pain or ache, weakness or muscle cramping that starts or worsens during treatment with statins and resolves when the statin is stopped. And, one of the statins causing muscle complaints was administered at the lowest approved dose*), who are receiving other lipid-lowering therapy (e.g., ezetimibe, BAS, niacin or gemfibrozil) and LDL reduction from untreated baseline is <50%, despite confirmed adherence to treatment, consideration can be given to a trial of alirocumab or evolocumab.

STORAGE:

- Alirocumab must be stored in the refrigerator (do not freeze) and kept in the outer carton and protected from light prior to use.
- Evolocumab may be refrigerated or stored at room temperature. If stored at room temperature, evolocumab should be used within 30 days.

Renewal Criteria (*All must be met prior to renewal of alirocumab*)

- Patient is tolerating alirocumab or evolocumab and is adherent to therapy.
- Patient has achieved a reduction in LDL of at least 40% from baseline (4-8 weeks after initiation or dose titration of alirocumab or evolocumab).
- Patient continues to have a significant reduction in LDL (with continuation of alirocumab or evolocumab) of at least 40% from baseline since initiation of PCSK9 inhibitor. LDL should be checked periodically with continued treatment with PCSK9 inhibitors (e.g., every 6 months).

Prepared: December 2015. Contact: Cathy Kelley, Pharm.D. VA Pharmacy Benefits Management Services. Revised Sept. 2016

References

1. Carlson B. Familial Hypercholesterolemia Captures Gene Test Controversies. *Biotechnology Healthcare* 2010;8-9. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2873730/pdf/bth07_1p008.pdf
2. ESC/EAS Guidelines for the Management of Dyslipidemias. The Task Force for the Management of Dyslipidemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), *Eur Heart J* 2011;32:1769-1818. <http://eurheartj.oxfordjournals.org/content/ehj/32/14/1769.full.pdf>
3. Diagnostic Criteria for Familial Hypercholesterolemia Using Simon Broome Register. http://heartuk.org.uk/files/uploads/documents/HUK_AS04_Diagnostic.pdf
4. Lambert G, Chatelais M, Petrides F, et al. Normalization of Low-Density Lipoprotein Receptor Expression in Receptor Defective Homozygous Familial Hypercholesterolemia by Inhibition of PCSK9 With Alirocumab. *J Am Coll Cardiol* 2014;64:2299-2300.
5. Stein EA, Honarpour H, Wasserman SM, et al. Effect of the Proprotein Convertase Subtilisin/Kevin Type 9 Monoclonal Antibody, AMG 145, in Homozygous Familial Hypercholesterolemia. *Circulation* 2013;128:2113-2120.
6. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with Evolocumab in Homozygous Familial Hypercholesterolemia (TESLA Part B): A Randomized, Double-Blind, Placebo-Controlled Trial. *Lancet* 2015;385:341-350.
7. FDA Review of Alirocumab (PRALUENT). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125559Orig1s000MedR.pdf (Accessed 11-3-15)
8. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and Safety of Alirocumab Versus Ezetimibe in Statin-Intolerant Patients, With a Statin Re-Challenge Arm: The ODYSSEY ALTERNATIVE Randomized Trial. *J Clin Lipidology* 2015;doi: 10.1016/j.jacl.2015.08.006. <http://www.lipidjournal.com/article/S1933-2874%2815%2900367-0/pdf> (Accessed 9-16-15)
9. Stoes E, Colquhoun D, Sullivan D, et al. Anti-PCSK9 Antibody Effectively Lowering Cholesterol in Patients With Statin Intolerance. The GAUSS-2 Randomized, Placebo-Controlled Phase 3 Trial of Evolocumab. *J Am Coll Cardiol*. 2014;63:2541-2548.
10. Gidding SS, Champagne MA, de Ferranti SD, et al. The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart Association. *Circulation* 2015. <http://circ.ahajournals.org/content/early/2015/10/28/CIR.000000000000297.full.pdf#page=1&view=FitH> (Accessed 12-15-15).