Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9 Inhibitor) (Alirocumab-preferred, Evolocumab-non-preferred) Criteria for Use June 2024

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 USE 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 the *PBM INTRAnet* site for further information.

Exclusion Criteria

If the answer to ANY item below is met, then the patient should NOT receive alirocumab or evolocumab.

- ☐ End-stage renal disease on dialysis
- ☐ Advanced heart failure with limited prognosis
- ☐ Severe comorbid non-cardiovascular condition that is expected to limit life expectancy
- ☐ Pregnant or lactating

Inclusion Criteria

One of the following criteria must be met.

- ☐ History of ASCVD[1]
- ☐ Severe primary hypercholesterolemia (e.g., HeFH[2], LDL-C[3] $\geq$ 190 mg/dL) without ASCVD[4]

[1]ASCVD=Atherosclerotic cardiovascular disease

[2]HeFH=Heterozygous familial hypercholesterolemia

[3]LDL-C=Low density lipoprotein cholesterol

[4]Refer to supplemental section for guidance on patients at high-risk but without ASCVD and LDL <190 mg/dL and discussion on statin intolerance.

Additional Inclusion Criteria

All of the following criteria must be met.

- ☐ Contraindication, intolerance to or insufficient LDL-C reduction with maximally tolerated dose of statin[5] and needs further LDL-C lowering to reduce ASCVD risk consistent with established guidelines.
- ☐ Contraindication, intolerance to or insufficient LDL-C reduction with ezetimibe and needs further LDL-C lowering to reduce ASCVD risk consistent with established guidelines.

[5]Maximally tolerated dose of statin may be none. Confirmed statin intolerance is intolerance to at least 2 statins, one at the lowest approved daily dose. Refer to supplemental information for guidance in patients who are statin intolerant.

Additional Inclusion Criteria-Select if Applicable

- ☐ For patients who can become pregnant: Counseling provided on potential risks vs benefits of treatment and the use of effective contraception during therapy.[6]

[6]However, if a patient becomes pregnant during treatment and a decision is made to continue therapy, providers are encouraged to report exposure since there are ongoing pregnancy safety studies for both drugs. Refer to the specific prescribing information for details.

Supplemental Information

Statins remain the treatment of choice for improving CV outcomes in both primary and secondary prevention.

There is limited evidence supporting a reduced risk for adverse cardiovascular disease events in patients taking PCSK9 inhibitors as monotherapy or in the absence of statins. Therefore, statins remain the treatment of choice for improving CV outcomes in both primary and secondary prevention. Statins augment the LDL-C lowering capability of PCSK9 inhibitors because statins upregulate LDL-C receptors while PCSK9 inhibitors block degradation of the LDL-C receptor. These actions result in a greater number of LDL-C receptors available to clear circulating LDL-C. Additionally, statins are believed to be associated with pleiotropic effects (e.g., reducing inflammation, improving endothelial function, decreasing oxidative stress, and stabilizing and regressing atherosclerotic plaques), benefitting patients beyond LDL-C lowering.

The following applies to patients with documented "statin intolerance" and established ASCVD or with severe primary hyperlipidemia (e.g., HeFH, LDL-C >190 mg/dL):

- Intolerance to statins should be documented and in practical terms is defined as a trial of at least 2 statins which resulted in intolerable 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 statins causing muscle complaints should have been tried at the lowest approved dose and a trial of alternate day dosing should be attempted. (See footnote and link below regarding information for addressing statin intolerance)
- Consider and address factors that may increase the risk for statin intolerance and non-statin causes of muscle symptoms (e.g., hypothyroidism, vitamin D deficiency, drug-drug interactions, excessive alcohol use, etc.)
- Those on lower than optimal statin doses should receive ezetimibe as necessary as second line treatment.
- For those who are on lower than optimal statin doses (including use of alternate day statin dosing) and are on ezetimibe, if the LDL reduction from untreated baseline is less than clinically desired and/or LDL-C goal (consistent with established guidelines) is not achieved, despite confirmed adherence to treatment, consideration can be given to using monoclonal antibody inhibitors of PCSK9.
- Finally, if a patient is completely intolerant of statin therapy (i.e., no statin can be used) and ezetimibe has not or is not expected to provide clinically desired LDL-C reduction from untreated baseline or achieve LDL-C goal (consistent with established guidelines), use of monoclonal antibody inhibitors of PCSK9 can be considered.

The following applies to patients with documented "statin intolerance" without established ASCVD and LDL-C <190 mg/dL:

- Ezetimibe, bile acid sequestrant (BAS) or the combination, should be utilized in appropriate candidates.
- In patients at high-risk for an event (e.g., diabetes mellitus, 10-year risk score ≥ 20%, presence of subclinical atherosclerosis by imaging including coronary artery calcium assessment and coronary CT), ezetimibe, BAS or the combination should be utilized in appropriate candidates. If LDL-C is not reduced by a clinically meaningful percentage from baseline (>30% or >50% based on risk assessment and clinical need) and/or LDL-C goals (consistent with established guidelines) are not reached, despite confirmed adherence, use of monoclonal antibody inhibitors of PCSK9 may be considered.

Refer to the following link for guidance on managing statin intolerance: National Academic Detailing Services - 10-1695_Dyslipidemia_Provider_StatinIntolerance_P97132 - GroupbyCampaign (sharepoint.com)

Prepared: Rev. June 2024. Contact: Cathy Kelley, PharmD, National Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services (12PBM)