This drug requires a written request for prior authorization. All requests for Praluent (alirocumab) require review by a pharmacist prior to final approval.

GUIDELINES FOR USE

INITIAL CRITERIA (NOTE: FOR RENEWAL CRITERIA, SEE BELOW)

1. Does the patient meet ALL of the following criteria:
   • Age is at least 18 years old
   • LDL cholesterol level is greater than 100mg/dL (LDL level within past 6 months) while patient is on maximal drug treatment and dietary therapy for at least 6 months
   • Praluent is prescribed by, or in consultation with a cardiologist, endocrinologist, or lipidologist
   • Praluent will not be used concurrently with Repatha
   • The patient has ONE of the following diagnoses:
     ▪ Diagnosis of heterozygous familial hypercholesterolemia (HeFH) as determined by meeting ONE of the following criteria:
       o Simon Broome diagnostic criteria for HeFH (definite) [example: genetic testing consistent with HeFH AND pretreatment baseline LDL cholesterol is greater than 190 mg/dL]
       o Dutch Lipid Network criteria for HeFH with a score of at least 6
     ▪ History of atherosclerotic cardiovascular disease as substantiated by hospital admission, imaging study, or surgical procedure (Examples of atherosclerotic cardiovascular disease include history of myocardial infarction or other acute coronary syndrome, coronary or other revascularization procedure, transient ischemic attack, or ischemic stroke; atherosclerotic peripheral arterial disease, or documented atherosclerotic disease such as coronary atherosclerosis, renal atherosclerosis, aortic aneurysm secondary to atherosclerosis, or carotid plaque with 50% or more stenosis)

If yes, continue to #2.
If no, do not approve

DENIAL TEXT: See the initial denial text at the end of the guideline

CONTINUED ON NEXT PAGE
ALIROCUMAB

INITIAL CRITERIA (CONTINUED)

2. Does the patient have a diagnosis of homozygous familial hypercholesterolemia?
   If yes, do not approve.
   **DENIAL TEXT:** See the initial denial text at the end of the guideline.
   If no, continue to #3.

3. Prior to Praluent, has the patient been taking maximal LDL-lowering drug treatment for at least 6 months that includes Zetia (ezetimibe) in combination with one of the following drugs:
   - the highest dose of a high intensity statin (e.g., atorvastatin 80mg daily, or rosuvastatin 40mg daily), **OR**
   - a maximally tolerated dose of atorvastatin or rosuvastatin with documentation regarding trials with atorvastatin 80mg daily, or rosuvastatin 40mg daily, **OR**
   - a maximally tolerated dose of any statin given that patient has had a previous trial of either atorvastatin 80mg or rosuvastatin 40mg, with prescriber’s documentation regarding length of previous trials of statins and reasons why each agent could not be tolerated
   If yes, continue to #4.
   If no, do not approve.
   **DENIAL TEXT:** See the initial denial text at the end of the guideline.

4. Does the patient intend to continue taking maximally tolerated statin (as defined in #3) once Praluent is started?
   If yes, approve for 12 weeks by HICL with a quantity limit of #2 syringes/pens per 28 days.
   If no, do not approve.
   **DENIAL TEXT:** See the initial denial text at the end of the guideline.

**CONTINUED ON NEXT PAGE**
ALIROCUMAB

INITIAL CRITERIA (CONTINUED)

INITIAL DENIAL TEXT: Our guideline for ALIROCUMAB requires that the patient is at least 18 years of age, has a LDL cholesterol level of greater than 100mg/dL within the past 6 months while on maximal drug and dietary therapy for at least 6 months, and has a diagnosis of heterozygous familial hypercholesterolemia or history of atherosclerotic cardiovascular disease. Patient must not have a diagnosis of homozygous familial hypercholesterolemia. Praluent must be prescribed by, or in consultation with a cardiologist, endocrinologist, or lipidologist. Praluent must not be used concurrently with Repatha. Diagnosis must include documentation as follows:

- **For the patients with heterozygous familial hypercholesterolemia**, diagnosis must be determined by meeting ONE of the following criteria:
  - Simon Broome diagnostic criteria for HeFH (definite) [example: genetic testing consistent with HeFH and pretreatment baseline LDL cholesterol is greater than 190 mg/dL]
  - Dutch Lipid Network criteria for HeFH with a score of at least 6
- **For patients with atherosclerotic cardiovascular disease**, diagnosis must be substantiated by hospital admission, imaging study, or surgical procedure. Additional guideline requirements apply.
  - Prior to Praluent, the patient must be taking maximal LDL-lowering drug treatment for at least 6 months that includes Zetia (ezetimibe) and ONE of the following drugs:
    - The highest dose of a high intensity statin (e.g., atorvastatin 80mg or rosuvastatin 40mg), OR
    - a maximally tolerated dose of atorvastatin or rosuvastatin with documentation regarding trials with the highest doses, OR
    - a maximally tolerated dose of any statin given that the patient has previously failed either atorvastatin 80mg or rosuvastatin 40mg and has documentation regarding length of previous trials of statins and reasons why each agent could not be tolerated.
  - Patient must continue therapy with maximally tolerated statin while using Praluent.

RENEWAL CRITERIA

1. Is the request for a patient who has had at least 12 weeks of Praluent treatment?
   
   If yes, continue to #2.
   If no, do not approve.
   
   DENIAL TEXT: See the renewal denial text at the end of the guideline.

CONTINUED ON NEXT PAGE
2. Are there any prescription claims for Repatha, Juxtapid, and/or Kynamro after the date of Praluent approval and first claim?
   If yes, do not approve.
   **DENIAL TEXT:** See the renewal denial text at the end of the guideline.
   If no, continue to #3.

3. Is the patient adherent to both statin therapy and Praluent?
   If yes, continue to #4.
   If no, do not approve.
   **DENIAL TEXT:** See the renewal denial text at the end of the guideline.

4. Does the patient have a diagnosis of heterozygous familial hypercholesterolemia and has had a LDL reduction of at least 35% from baseline, at or after 12 weeks of treatment?
   If yes, **approve for 12 months by HICL with a quantity limit of #2 syringes/pens per 28 days**
   If no, continue to #5.

5. Does the patient have a diagnosis of atherosclerotic cardiovascular disease and has had a LDL reduction of at least 40% from baseline, at or after 12 weeks of treatment?
   If yes, **approve for 12 months by HICL with a quantity limit of #2 syringes/pens per 28 days.**
   If no, do not approve.
   **DENIAL TEXT:** See the renewal denial text at the end of the guideline.

**RENEWAL DENIAL TEXT:** Our guideline for **ALIROCUMAB** renewal requires that the patient has had at least 12 weeks of therapy, is adherent to both statin therapy and Praluent during the regimen, has no prescription claims for Repatha, Juxtapid, and/or Kynamro after the date of Praluent approval and first claim, and an LDL reduction while on therapy as noted below. Additional guideline requirements apply.

- **For the diagnosis of heterozygous familial hypercholesterolemia,** approval requires a LDL reduction of at least 35% from baseline, at or after 12 weeks of alirocumab therapy.
- **For the diagnosis of atherosclerotic cardiovascular disease,** approval requires an LDL reduction of at least 40% from baseline, at or after 12 weeks of alirocumab therapy.

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ALIROCUMAB

RATIONALE
Promote appropriate utilization of Praluent based on FDA approved indication.

FDA APPROVED INDICATIONS
Praluent is a PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) inhibitor antibody indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol.

DOSAGE
The recommended starting dose for Praluent is 75 mg administered subcutaneously once every 2 weeks, since the majority of patients achieve sufficient LDL-C reduction with this dosage. If the LDL-C response is inadequate, the dosage may be increased to the maximum dosage of 150 mg administered every 2 weeks.

Measure LDL-C levels within 4 to 8 weeks of initiating or titrating Praluent, to assess response and adjust the dose, if needed.

OTHER INFORMATION

EFFICACY
The efficacy of Praluent was evaluated in five multi-center, double-blind, placebo-controlled trials which enrolled 3499 patients (36% of patients had heterozygous familial hypercholesterolemia [HeFH] and 54% had clinical atherosclerotic cardiovascular disease without a diagnosis of FH). The diagnosis of HeFH was made by either genotyping or clinical criteria (using the Simon Broome or WHO/Dutch Lipid Network Criteria). All patients were receiving a maximally tolerated dose of a statin, with or without other lipid-modifying therapies. Three studies (FH I, FH II, and ODYSSEY COMBO I) used an initial dose of 75mg every 2 weeks (Q2W) followed by criteria-based up-titration to 150mg Q2W at week 12 for patients who did not achieve their pre-defined target LDL-C at week 8. The majority of patients (57-83%) did not require up-titration. The other two studies (ODYSSEY LONG TERM and ODYSSEY HIGH FH) only used a 150mg Q2W dose. The FH I, FH II, and ODYSSEY HIGH FH were conducted exclusively in patients with HeFH.

All trials used a primary endpoint of mean percent change in LDL-C from baseline that was measured at week 24 (all trials were at least 52 weeks in duration). For the primary endpoint, results for the absolute treatment effect are as follows:

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### OTHER INFORMATION (CONTINUED)

### EFFICACY (CONTINUED)

Table 1: Praluent clinical trials- primary endpoint and results for the absolute treatment effect

<table>
<thead>
<tr>
<th>Study</th>
<th>Praluent dosing</th>
<th>Absolute treatment effect of Praluent (difference between placebo and Praluent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ODYSSEY LONG TERM (Study 1)</td>
<td>Praluent 150mg Q2W</td>
<td>-58% (95% CI: -61%, -56%; p-value &lt;0.0001)</td>
</tr>
<tr>
<td>ODYSSEY COMBO I (Study 2)</td>
<td>Praluent 75mg or 150mg Q2W</td>
<td>-43% (95% CI: -50%, -35%; p-value &lt;0.0001)</td>
</tr>
<tr>
<td>FH I (Study 3) &amp; FH II (Study 4)</td>
<td>Praluent 75mg or 150mg Q2W</td>
<td>-54% (95% CI: -59%, -50%; p-value &lt;0.0001)</td>
</tr>
<tr>
<td>ODYSSEY HIGH FH (Study 5)</td>
<td>Praluent 150mg Q2W</td>
<td>-36% (95% CI: -49%, -24%; p-value &lt;0.0001)</td>
</tr>
</tbody>
</table>

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OTHER INFORMATION (CONTINUED)
EFFICACY (CONTINUED)
Table 2: ODYSSEY LONG TERM Study - Effects of alirocumab on LDL-lowering, secondary lipid variables, and rates of adjudicated cardiovascular events.

<table>
<thead>
<tr>
<th></th>
<th>Alirocumab</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in LDL-C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean percentage change in calculated LDL-C from baseline to week 24</td>
<td>-61%</td>
<td>0.8%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean percentage change in calculated LDL-C from baseline to week 78</td>
<td>-52.4%</td>
<td>3.6%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Mean absolute LDL-C level at week 24</td>
<td>48mg/dL</td>
<td>119mg/dL</td>
<td>N/A</td>
</tr>
<tr>
<td>Patients meeting LDL-C goal of &lt;70mg/dL at week 24</td>
<td>79.3%</td>
<td>8.0%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Non-LDL lipid end points, percentage change (secondary lipid variables)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in non-HDL cholesterol from baseline to week 24</td>
<td>-51.6% +/- 0.6</td>
<td>0.7% +/- 0.9</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Change in Apo lipoprotein B from baseline to week 24</td>
<td>-52.8% +/-0.7</td>
<td>1.2% +/-1.0</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Change in total cholesterol from baseline to week 24</td>
<td>-37.8% +/-0.5</td>
<td>-0.3% +/-0.7</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Change in lipoprotein(a) from baseline to week 24</td>
<td>-29.3% +/-0.7</td>
<td>-3.7% +/-1.0</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Change in fasting triglycerides from baseline to week 24</td>
<td>-15.6% +/-0.8</td>
<td>1.8% +/-1.2</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Change in HDL cholesterol from baseline to week 24</td>
<td>4.0% +/-0.4</td>
<td>-0.6% +/-0.5</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Change in Apolipoprotein A1 from baseline to week 24</td>
<td>4.0% +/-0.4</td>
<td>1.2% +/-0.6</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Cardiovascular adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positively adjudicated cardiovascular events</td>
<td>4.6%</td>
<td>5.1%</td>
<td>0.68</td>
</tr>
<tr>
<td>Adjudicated major cardiovascular events in post-hoc analysis</td>
<td>1.7%</td>
<td>3.3%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

SAFETY
The only contraindication for Praluent is for patients with a history of serious hypersensitivity to the product itself. Serious allergic events have been reported with Praluent treatment and may include pruritus, rash, urticaria, hypersensitivity vasculitis, and/or hypersensitivity reactions requiring hospitalization. Allergic reactions were reported in 8.6% of patients treated with Praluent versus 7.8% of patients in the placebo group. Allergic reactions were cited as the top reason for discontinuing Praluent (0.6% of Praluent discontinuations versus 0.2% in the placebo group) due to adverse drug reactions (ADRs).

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SAFETY (CONTINUED)
The most common adverse effects of Praluent (occurring in 5% or greater of clinical trial participants and more frequently than placebo) are injection site reactions, influenza, and nasopharyngitis. Injection site reactions are more likely to occur in patients who develop anti-drug antibodies (ADA). The development of ADA occurred in 4.8% of Praluent patients (versus 0.6% for control). Patients with anti-drug antibodies had a higher incidence of injection site reactions (10.2%) compared with patients who did not develop anti-drug antibodies (5.9%). Development of neutralizing antibodies occurred in 1.2% of patients treated with Praluent; no patients in the control group developed neutralizing antibodies. Of patients who developed neutralizing antibodies, 0.3% both tested positive for neutralizing antibodies and experienced a prolonged loss of efficacy. The long term consequences of continued treatment of Praluent while neutralizing antibodies are present is not known.

Table 3: Praluent adverse reactions (from Praluent prescribing information)

<table>
<thead>
<tr>
<th>Most common adverse reactions (reported in at least 2% of participants receiving Praluent)</th>
<th>Praluent (n=2476)</th>
<th>Placebo (n=1276)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>11.3%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>7.2%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Influenza</td>
<td>5.7%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>4.8%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.7%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>4.3%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4.2%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>3.1%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>3.0%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Cough</td>
<td>2.5%</td>
<td>2.3%</td>
</tr>
<tr>
<td>Contusion</td>
<td>2.1%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>2.1%</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

Less common adverse effects

| Allergic reactions                           | 8.6%            | 7.8%            |
| Neurocognitive Events                        | 0.8%            | 0.7%            |
| Confusion or Memory impairiment              | 0.2%            | 0.1%            |
| Liver Enzyme Abnormalities                   | 2.5%            | 1.8%            |

Analysis of both placebo-controlled and active-controlled trials showed that 796 patients receiving Praluent had LDL levels less than 25mg/dL and 288 patients had LDL levels less than 15mg/dL. Adverse effects of very low LDL levels were not identified in Praluent clinical trials, but the long-term consequences of very low LDL levels are not known at this time.

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SAFETY (CONTINUED)
Praluent has not been studied in human pregnancy and lactation studies. Based on the human data from other human monoclonal antibodies, it is unlikely to cross the placenta in the first trimester; however, it is likely to cross the placenta in increasing amounts in the second and third trimester. There is no information regarding the presence of Praluent in human milk, the effects on the breastfed infant, or the effects on milk production. However, published data involving human IgG suggests that substantial amounts of IgG antibodies do not reach the infant’s circulation.

No dose adjustment is required in patients with mild or moderate renal or hepatic impairment. No data is available regarding use during severe renal or hepatic impairment. No differences in safety and efficacy were seen between geriatric and younger adults. Safety and efficacy has not been established in pediatric patients.

REFERENCES