This drug requires a written request for prior authorization. All requests for Repatha (evolocumab) 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 the past 6 months) while patient is on maximal drug treatment and dietary therapy (low fat diet) for at least 6 months
   - Repatha is prescribed by, or in consultation with a cardiologist, endocrinologist, or lipidologist
   - Repatha will not be used concurrently with Praluent
   - 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, continue to #4.

CONTINUED ON NEXT PAGE
2. Prior to Repatha, has the patient been taking a maximal LDL-lowering drug regimen consistently for at least 6 months that includes a combination of ezetimibe and **ONE** of the following drugs:
   - the highest dose of a high intensity statin (e.g., atorvastatin 80mg daily, or rosuvastatin 40mg daily)
   - a maximally tolerated dose of atorvastatin or rosuvastatin with documentation regarding trials with atorvastatin 80mg daily, or rosuvastatin 40mg daily
   - 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 #3.
   If no, do not approve.

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

3. Does the patient intend to continue taking maximal statin once Repatha is started?

   If yes, **approve for 12 weeks by GPID with a quantity limit up to #2 syringes/pens per 28 days for Repatha 140mg [420mg syringe dosage form not available at this time].**

   **APPROVAL TEXT:** Initial approval is for 12 weeks. Renewal criteria will require that the patient demonstrate continued adherence to Repatha and statin and an LDL reduction to demonstrate response to Repatha therapy.

   If no, do not approve.

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

4. Does the patient meet **ALL** of the following criteria:
   - Age is at least 13 years old
   - LDL cholesterol level is greater than 160mg/dL (LDL level within the past 6 months) while patient is on maximal drug treatment and dietary therapy (low fat diet) for at least 6 months
   - Repatha is prescribed by, or in consultation with a cardiologist, endocrinologist, or lipidologist
   - Repatha will not be used concurrently with Praluent
   - The patient has a diagnosis of homozygous familial hypercholesterolemia (HoFH) as determined by meeting **ONE** of the following criteria:
     - Simon Broome diagnostic criteria for HoFH (definite) [example: genetic testing consistent with HoFH and pretreatment baseline LDL cholesterol is greater than 190 mg/dL]
     - Dutch Lipid Network criteria for HoFH with a score of at least 8

   If yes, continue to #5.
   If no, do not approve.

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

**CONTINUED ON NEXT PAGE**
5. Prior to Repatha treatment, has the patient been taking a maximal LDL-lowering drug regimen consistently for at least 6 months that includes a maximally tolerated statin in combination with ezetimibe, as defined by ONE of the following:
   • The highest dose of a high intensity statin (e.g., atorvastatin 80mg daily, or rosvastatin 40mg daily)
   • A maximally tolerated dose of atorvastatin or rosuvastatin with documentation regarding trials with atorvastatin 80mg daily, or rosvastatin 40mg daily
   • 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 #9.
   If no, continue to #6.

6. Does the patient have an absolute contraindication to statin therapy (active, decompensated liver disease, nursing female, pregnancy or plans to become pregnant, hypersensitivity reaction), AND is being treated consistently for at least 6 months with maximal lipid-lowering therapy with another lipid-lowering agent (e.g., ezetimibe, niacin, bile acid sequestrants, Kynamro, Juxtapid), or receiving regular LDL apheresis treatments?

   If yes, continue to #9.
   If no, continue to #7.

7. Prior to Repatha, is the patient being treated consistently for at least 6 months with maximal lipid-lowering therapy with another lipid-lowering agent (e.g., ezetimibe, bile acid sequestrants, niacin, Juxtapid, Kynamro) or receiving regular LDL apheresis treatments due to failing at least 2 statin agents (at least one of which must be a high-intensity statin regimen)?

   If yes, continue to #8.
   If no, do not approve.

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

INITIAL CRITERIA (CONTINUED)

8. Is there documentation of statin failure which includes ALL of the following:
   - Documentation of severe and intolerable adverse effects that have occurred with every trial of statin, and other potential causes were ruled out (low vitamin D levels, sudden increase in intense or prolonged physical activity, drug interactions with statins, or other metabolic or inflammatory causes)
   - Patient tried alternate dosing strategies such as every-other-day statin dosing or twice weekly dosing
   - Documentation of at least ONE of the following lab values or incidents:
     o CK increase to 10 times upper limit of normal during statin therapy
     o LFTs increase to 3 times upper limit of normal during statin therapy
     o Hospitalization due to severe adverse event such as rhabdomyolysis during statin therapy
     o Severe muscle weakness leading to temporary disability, fall, or inability to use a major muscle group during statin therapy (e.g., unable to stand from a seated position or inability to exit a motor vehicle without assistance.)

If yes, continue to #9.
If no, do not approve.

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

9. Does the patient intend to continue taking statin once Repatha is started (or if statin intolerant or contraindicated, continue on apheresis or other lipid-lowering agent that does not include Juxtapid or Kynamro)?

   If yes, approve for 12 weeks by GPIID with a quantity limit up to #3 syringes/pens per 28 days for Repatha 140mg [420mg syringe dosage form not available at this time].

   APPROVAL TEXT: Initial approval is for 12 weeks. Renewal criteria will require that the patient demonstrates continued adherence to Repatha and statin or apheresis (or for statin intolerant patients, continued adherence to Repatha and another lipid-lowering agent, with the exception of Juxtapid or Kynamro). Since the safety and efficacy of Kynamro or Juxtapid in combination with PCSK9 inhibitors has not been evaluated, the Repatha guideline will require patients to discontinue therapy with Kynamro or Juxtapid prior to renewal in order to receive additional approval after the 12 weeks initial approval. Patients taking Kynamro or Juxtapid are required to continue another lipid-lowering therapy (e.g., ezetimibe) or apheresis, AND an LDL reduction to demonstrate response to Repatha therapy.

If no, do not approve.

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

CONTINUED ON NEXT PAGE
INITIAL CRITERIA (CONTINUED)

INITIAL DENIAL TEXT: Our guideline for EVOLOCUMAB requires that Repatha (evolocumab) is prescribed by, or in consultation with a cardiologist, endocrinologist, or lipidologist, AND that it is not used concurrently with Praluent (alirocumab). Additional guideline requirements apply.

For patients with heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic cardiovascular disease, ALL of the following criteria must be met:

- Age is at least 18 years old, AND
- LDL cholesterol level is greater than 100mg/dL (LDL level within the past 6 months) while patient is on maximal drug treatment and dietary therapy (low fat diet) for at least 6 months, AND
- Diagnosis must be determined or substantiated by the following:
  - For heterozygous familial hypercholesterolemia, ONE of the following criteria must be met:
    - 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 atherosclerotic cardiovascular disease, diagnosis must be substantiated by hospital admission, imaging study, or surgical procedure.
- Prior to Repatha, patient must have been taking a maximal LDL-lowering drug regimen consistently for at least 6 months that includes a combination of ezetimibe and ONE of the following drugs:
  - the highest dose of a high intensity statin (e.g., atorvastatin 80mg daily, or rosvastatin 40mg daily), OR
  - a maximally tolerated dose of atorvastatin or rosvastatin with documentation regarding trials with atorvastatin 80mg daily, or rosvastatin 40mg daily, OR
  - a maximally tolerated dose of any statin given that patient has had a previous trial of either atorvastatin 80mg or rosvastatin 40mg, with prescriber's documentation regarding length of previous trials of statins and reasons why each agent could not be tolerated
- Patient intends to continue maximal statin once Repatha is started.

For patients with homozygous familial hypercholesterolemia (HoFH), ALL of the following criteria must be met:

- Age is at least 13 years old, AND
- LDL cholesterol level is greater than 160mg/dL (LDL level within the past 6 months) while patient is on maximal drug treatment and dietary therapy (low fat diet) for at least 6 months, AND
- Diagnosis of HoFH must be determined by meeting ONE of the following criteria:
  - Simon Broome diagnostic criteria for HoFH (definite) [example: genetic testing consistent with HoFH and pretreatment baseline LDL cholesterol is greater than 190 mg/dL]
  - Dutch Lipid Network criteria for HoFH with a score of at least 8

(Initial denial text continued on next page)
EVOLOCUMAB

INITIAL CRITERIA (CONTINUED)

- **For statin-tolerant patients:**
  - Prior to Repatha, patient must have been taking a maximal LDL-lowering drug regimen consistently for at least 6 months that includes a combination of ezetimibe and **ONE** of the following drugs:
    - the highest dose of a high intensity statin (e.g., atorvastatin 80mg daily, or rosvuastatin 40mg daily), **OR**
    - a maximally tolerated dose of atorvastatin or rosvuastatin with documentation regarding trials with atorvastatin 80mg daily, or rosvuastatin 40mg daily, **OR**
    - a maximally tolerated dose of any statin given that patient has had a previous trial of either atorvastatin 80mg or rosvuastatin 40mg, with prescriber’s documentation regarding length of previous trials of statins and reasons why each agent could not be tolerated
  - Patient intends to continue maximal statin once Repatha is started

- **For statin-intolerant patients or those with contraindication to statins:**
  - Patient must have an absolute contraindication to statins or provide documentation of statin failure which includes the following:
    - Patient has previously failed at least 2 statin agents, at least one of which must be a high-intensity statin regimen
    - Severe and intolerable adverse effects, with other potential causes ruled out (low vitamin D levels, sudden increase in intense or prolonged physical activity, drug interactions with statins, other metabolic or inflammatory causes), **AND**
    - Failed rechallenge with a second statin agent, including alternate dosing strategies such as every-other-day statin dosing or twice weekly dosing, **AND**
    - **ONE** of the following lab values or incidents:
      - CK level exceeds 10 times upper limit of normal
      - LFTs exceed 3 times upper limit of normal
      - Hospitalization due to severe adverse event such as rhabdomyolysis
      - Severe muscle weakness leading to temporary disability, fall, or inability to use a major muscle group (e.g., unable to get up)
  - Prior to Repatha, patient must have been treated consistently for at least 6 months with maximal lipid-lowering therapy with another lipid-lowering agent (e.g., ezetimibe, bile acid sequestrants, niacin, Juxtapid, Kynamro), or receiving regular LDL apheresis treatments.
  - Patient intends to continue on apheresis or other lipid-lowering agent that does not include Juxtapid or Kynamro once Repatha is started. Since the safety and efficacy of Kynamro or Juxtapid in combination with PCSK9 inhibitors has not been evaluated, the Repatha guideline requires patients to discontinue therapy with Kynamro or Juxtapid prior to renewal in order to receive additional approval after the 12 weeks initial approval. Patients taking Kynamro or Juxtapid are required to continue another lipid-lowering therapy (e.g., ezetimibe) or apheresis.

CONTINUED ON NEXT PAGE
EVOLOCUMAB

GUIDELINES FOR USE (CONTINUED)

RENEWAL CRITERIA

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

2. Are there any prescription claims for Praluent after the date of Repatha 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 taking Juxtapid (lomitapide) or Kynamro (mipomersen)?
   If yes, send to Medical Director for further review.
   **DENIAL TEXT:** See the renewal denial text at the end of the guideline.
   If no, continue to #4.

4. Is the patient adherent to both Repatha and maximally tolerated statin therapy (or, for statin intolerant patients with HoFH, patient is adherent to Repatha and other lipid-lowering therapy which includes Zetia (ezetimibe), niacin, bile acid sequestrants, or LDL apheresis treatment)?
   If yes, continue to #5.
   If no, do not approve.
   **DENIAL TEXT:** See the renewal denial text at the end of the guideline.

5. Does the patient have a diagnosis of heterozygous familial hypercholesterolemia (HeFH) 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 GPID with a quantity limit of #2 syringes per 28 days for Repatha 140mg** [420mg syringe dosage form not available at this time].
   If no, continue to #6.

**CONTINUED ON NEXT PAGE**
EVOLOCUMAB

RENEWAL CRITERIA (CONTINUED)

6. Does the patient have a diagnosis of atherosclerotic cardiovascular disease (ASCVD) and has had an LDL reduction of at least 40% from baseline, at or after 12 weeks of treatment?

    If yes, approve for 12 months by GPID with a quantity limit of #2 syringes per 28 days for Repatha 140mg [420mg syringe dosage form not available at this time]. If no, continue to #7.

7. Does the patient have a diagnosis of homozygous familial hypercholesterolemia (HoFH) and has had an LDL reduction of at least 20% from baseline, at or after 12 weeks of treatment?

    If yes, approve for 12 months by GPID with a quantity limit of #3 syringes per 28 days for Repatha 140mg [420mg syringe dosage form not available at this time]. If no, do not approve.

DENIAL TEXT: See the renewal denial text at the end of the guideline.

RENEWAL DENIAL TEXT: Our guidelines for EVOLOCUMAB renewal require that the patient is not concurrently using Praluent, has had at least 12 weeks of therapy, is adherent to statin and Repatha regimen during therapy (or, if statin-intolerant, patient is adherent to Repatha and apheresis or other lipid-lowering agent, with the exception of Juxtapid or Kynamro), and has an LDL reduction on therapy as noted below.

- For the diagnosis of heterozygous familial hypercholesterolemia, approval requires an LDL reduction of at least 35% from baseline after evolocumab therapy for 12 weeks.
- For the diagnosis of homozygous familial hypercholesterolemia, approval requires an LDL reduction of at least 20% from baseline after evolocumab therapy for 12 weeks.
- For the diagnosis of atherosclerotic cardiovascular disease, approval requires an LDL reduction of at least 40% after evolocumab therapy for 12 weeks.

Since the safety and efficacy of Kynamro or Juxtapid in combination with PCSK9 inhibitors has not been evaluated, the Repatha guideline requires patients to have discontinued therapy with Kynamro or Juxtapid prior to renewal in order to receive additional approval after the 12 weeks initial approval. Patients taking Kynamro or Juxtapid are required to continue another lipid-lowering therapy (e.g., ezetimibe) and/or apheresis with Repatha.

RATIONALE
Promote appropriate utilization of Repatha based on FDA approved indication and appropriate clinical criteria.

CONTINUED ON NEXT PAGE
EVOLOCUMAB

FDA APPROVED INDICATIONS
For use 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 lowering of low density lipoprotein cholesterol (LDL-C). Repatha is also approved for use with other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

Limitations of Use:
- The effect of Repatha on cardiovascular morbidity and mortality has not been determined.

Efficacy
The efficacy of Repatha for patients with primary hyperlipidemia and clinical atherosclerotic cardiovascular disease (CVD) was studied in two multicenter, double-blind, randomized, controlled trials (Study 1 and Study 2).

In Study 1 patients received an open-label, specific statin regimen over a 4 week lipid stabilization period, then were randomized to either Repatha 140mg subcutaneously every 2 weeks (q2wk), Repatha 420mg subcutaneously every 4 weeks (q4wk), or placebo for 12 weeks. Repatha or placebo was add-on therapy to daily statin treatment (atorvastatin 80mg, rosuvastatin 40mg, or simvastatin 40mg daily). Patient characteristics included mean age 63 years (range 32-80 years), 45% were 65 years or older, 33% female, 98% Caucasian, 5% Hispanic or Latino, 2% of African descent, and less than 1% Asian. After 4 weeks of lipid stabilization period (with statin treatment), the mean baseline LDL cholesterol was 108mg/dL. After 12 weeks of treatment the difference in percentage change in LDL-C between placebo- and Repatha-treated groups was -71%. The mean percentage change from baseline in the treatment groups are provided below in figure 1.

Study 2 was placebo-controlled. All 139 patients enrolled received background lipid-lowering therapy with atorvastatin 80mg daily, with or without ezetimibe 10mg daily; after stabilization on background therapy they were randomized to either placebo or Repatha 420mg once monthly. Patient characteristics included mean age 59 years (range 35-75 years), 25% were 65 years or older, 40% female, 80% Caucasian, 5% Asian, 3% of African descent, and <1% Hispanic or Latino. After stabilization on background statin treatment with or without ezetimibe, the mean baseline LDL cholesterol was 105mg/dL. The difference between Repatha 420mg and placebo groups in mean percentage change in LDL-C from baseline to Week 52 was -54%.

CONTINUED ON NEXT PAGE
EVOLOCUMAB

EFFICACY (CONTINUED)
The efficacy of Repatha in patients with familial hypercholesterolemia was evaluated in Study 3 (RUTHERFORD-2) and Study 4 (TESLA Part B). Study 3 and Study 4 were multi-center, double-blind, randomized, placebo-controlled, 12-week trials. Study 3 enrolled 329 patients with HeFH on statins, with or without other lipid-lowering agents, and randomized patients to either Repatha 140mg q2wk, Repatha 420mg q4wk, or placebo. Study 4 enrolled 49 patients with HoFH (not on lipid apheresis therapy).

In Study 3 100% of patients had HeFH (diagnosis by Simon Broome criteria), and 38% of patients also had ASCVD. Patient characteristics in Study 3 included mean age 51 years (range 19-79 years), 15% were 65 years or older, 42% female, 90% Caucasian, 5% Asian, and 1% of African descent. The mean baseline LDL cholesterol was 156mg/dL; approximately 76% of patients were on high intensity statin therapy at the start of the study. The difference between Repatha 140mg and placebo groups in mean percentage change in LDL-C from baseline to Week 12 was -61%. The difference between Repatha 420mg and placebo groups in mean percentage change in LDL-C from baseline to Week 12 was -60%.

Figure 1: Study 1- Effect of Repatha on LDL cholesterol in patients with atherosclerotic CVD when combined with statins, mean percentage change from baseline to week 12

[From Repatha Prescribing Information]

CONTINUED ON NEXT PAGE
EFFICACY (CONTINUED)
In Study 4, all patients had a diagnosis of HoFH, confirmed by genetic testing or a clinical diagnosis based on a history of untreated LDL cholesterol above 500mg/dL with either a xanthoma before 10 years of age or evidence of HeFH in both parents. Patients were randomized to Repatha 420mg once monthly or placebo in combination with other lipid-lowering therapies (statins, ezetimibe). Patient characteristics in Study 4 included mean age 31 years, 49% female, 30% were adolescents age 13-17, 90% Caucasian, 4% Asian, and 6% other race. The mean baseline LDL cholesterol prior to start of the study drug was 349 mg/dL; all patients were on atorvastatin or rosuvastatin and 92% were on ezetimibe at the start of the study. The difference between Repatha 420mg and placebo groups in mean percentage change in LDL-C from baseline to Week 12 was -31.

Table 1: Effect of Repatha on lipid parameters in patients in Study 1, Study 2, Study 3, and Study 4 (Mean percentage change from baseline to Week 12, except where noted) [From Repatha Prescribing Information]

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>LDL-C</th>
<th>Non HDL-C</th>
<th>Apo B</th>
<th>Total Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1 – Patients with ASCVD on atorvastatin 80mg, rosuvastatin 40mg, or simvastatin 40mg daily (Mean percentage change from baseline to Week 12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo q2wk (n=42)</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Repatha 140mg q2wk (n=105)</td>
<td>-64</td>
<td>-56</td>
<td>-49</td>
<td>-38</td>
</tr>
<tr>
<td>Mean difference from placebo (95% CI)</td>
<td>-71 (-81,-61)</td>
<td>-58 (-67,-49)</td>
<td>-55 (-62,-47)</td>
<td>-42 (-48,-36)</td>
</tr>
<tr>
<td>Placebo q4wk (n=44)</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Repatha 420mg q4wk (n=105)</td>
<td>-58</td>
<td>-47</td>
<td>-46</td>
<td>-32</td>
</tr>
<tr>
<td>Mean difference from placebo (95% CI)</td>
<td>-63 (-76,-50)</td>
<td>-52 (-63,-41)</td>
<td>-49 (-58,-39)</td>
<td>-36 (-43,-28)</td>
</tr>
<tr>
<td>Study 2 – Patients with ASCVD on atorvastatin 80mg with or without ezetimibe 10mg daily (Mean percentage change from baseline to Week 52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo q4wk (n=44)</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Repatha 420mg q4wk (n=95)</td>
<td>-52</td>
<td>-41</td>
<td>-40</td>
<td>-28</td>
</tr>
<tr>
<td>Mean difference from placebo (95% CI)</td>
<td>-54 (-65,-42)</td>
<td>-44 (-56,-32)</td>
<td>-40 (-50,-30)</td>
<td>-31 (-39,-24)</td>
</tr>
<tr>
<td>Study 3 (RUTHERFORD-2) – Patients with HeFH (Mean percentage change from baseline to Week 12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment group</td>
<td>LDL-C</td>
<td>Non HDL-C</td>
<td>Apo B</td>
<td>Total Cholesterol</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------</td>
<td>-----------</td>
<td>--------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Placebo q2wk (n=54)</td>
<td>-1</td>
<td>-1</td>
<td>-1</td>
<td>-2</td>
</tr>
<tr>
<td>Repatha 140mg q2wk (n=110)</td>
<td>-62</td>
<td>-56</td>
<td>-49</td>
<td>-42</td>
</tr>
<tr>
<td>Mean difference from placebo (95% CI)</td>
<td>-61 (-67, -55)</td>
<td>-54 (-60,-49)</td>
<td>-49 (-54,-43)</td>
<td>-40 (-45,-36)</td>
</tr>
<tr>
<td>Placebo q4wk (n=55)</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Repatha 420mg q4wk (n=110)</td>
<td>-56</td>
<td>-49</td>
<td>-44</td>
<td>-37</td>
</tr>
<tr>
<td>Mean difference from placebo (95% CI)</td>
<td>-60 (-68, -52)</td>
<td>-53 (-60,-46)</td>
<td>-48 (-55,-41)</td>
<td>-39 (-45,-33)</td>
</tr>
</tbody>
</table>

**Study 4 (TESLA Part B) – Patients with HoFH (Mean percentage change from baseline to Week 12)**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>LDL-C</th>
<th>Non HDL-C</th>
<th>Apo B</th>
<th>Total Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo q4wk (n=16)</td>
<td>9</td>
<td>8</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Repatha 420mg q4wk (n=33)</td>
<td>-22</td>
<td>-20</td>
<td>-17</td>
<td>-17</td>
</tr>
<tr>
<td>Mean difference from placebo (95% CI)</td>
<td>-31 (-44,-18)</td>
<td>-28 (-41,-16)</td>
<td>-21 (-33,-9)</td>
<td>-25 (-36,-14)</td>
</tr>
</tbody>
</table>

CONTINUED ON NEXT PAGE
EVOLOCUMAB

Efficacy (Continued)
The results of two extension studies, OSLER-1 and OSLER-2, currently provide longer-term data for the efficacy and safety of Repatha. Additional information will be available when FOURIER, an outcomes trial with 27,500 patients; the estimated completion is in 2017. The OSLER studies were two open-label, randomized extension studies that enrolled 4465 patients who had completed a parent trial for Repatha (DESCARTES, MENDEL-1, MENDEL-2, LAPLACETIMI 57, LAPLACE-2, GAUSS-1, GAUSS-2, RUTHERFORD 1 & 2, YUKAWA-1, and THOMAS 1 & 2). Patients were randomized to receive Repatha 140mg q2wk or Repatha 420mg q4wk with standard therapy, or standard therapy alone. Standard therapy was based on local guidelines for treatment of LDL-C. Approximately 70% of patients in the study were on statin therapy; 26.7% (Repatha treatment group) to 27.9% (standard therapy group) were on a high intensity statin, and 12.6% (Repatha treatment group) to 15.9% (standard therapy group) were on ezetimibe. Participants were followed for a median of 11.1 months. Repatha led to a 61% reduction of LDL-C as compared to the standard therapy group. The rate of cardiovascular events at one year was significantly lower for the Repatha-treated group (0.95%) compared to the standard therapy group (2.18%) (HR 0.47, 95% CI 0.28 to 0.78, p=0.003).

Safety
Repatha is contraindicated for patients with a history of serious hypersensitivity reaction to Repatha. The most common adverse effects of Repatha (occurring in greater than 5% of clinical trial participants and more frequently than placebo) are nasopharyngitis, injection site reactions, influenza, back pain, and upper respiratory tract infection. Allergic reactions occurred in 5.1% of patients on Repatha versus 4.6% of patients on placebo, and included rash, eczema, erythema and urticaria. Injection site reactions occurred in 3.2% of Repatha-treated patients versus 3.0% of placebo-treated patients.

The development of binding antibodies occurred in 0.1% of Repatha patients, based on screening by an electrochemiluminescent bridging screening immunoassay for the detection of binding anti-drug antibodies. No patients in clinical trials tested positive for neutralizing antibodies. Detection of antibody formation may vary based on the sensitivity and specificity of the assay, as well as assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. Thus, comparison of the incidence of antibodies for Repatha with the incidence of antibodies to other PCSK9 inhibitor products may be misleading.

CONTINUED ON NEXT PAGE
EVOLOCUMAB

SAFETY (CONTINUED)

Table 2: Repatha adverse reactions - safety data from seven pooled 12-week studies (from Repatha prescribing information)

<table>
<thead>
<tr>
<th></th>
<th>Repatha (n=2052) (140mg &amp; 420mg doses)</th>
<th>Placebo (n=1224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common adverse reactions (reported in greater than 1% of participants receiving Repatha)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4.0%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Back pain</td>
<td>2.3%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>2.1%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1.8%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.8%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.6%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>1.3%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1.3%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Cough</td>
<td>1.2%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Influenza</td>
<td>1.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Contusion</td>
<td>1.0%</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

Table 3: Select adverse events observed in the OSLER clinical trial

<table>
<thead>
<tr>
<th></th>
<th>Repatha (n=2976)</th>
<th>Standard therapy group (n=1489)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive Events *</td>
<td>0.9%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Liver Enzyme Abnormalities (ALT or AST &gt;3 times upper limit of normal at any visit after baseline)</td>
<td>1.0%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Creatine kinase greater than 5 times upper limit of normal at any visit after baseline</td>
<td>0.6%</td>
<td>1.1%</td>
</tr>
</tbody>
</table>

* = Neurocognitive events were delirium/confusion, cognitive and attention disorders or disturbances, dementia and amnestic conditions, disturbances in thinking and perception, and mental impairment disorders.

Analysis of both placebo-controlled and active-controlled trials as well as open-label extension studies showed that 1609 patients receiving Repatha had LDL levels less than 25mg/dL. Adverse effects of very low LDL levels were not identified in Repatha clinical trials, however, the long-term consequences of very low LDL levels are not known at this time.

CONTINUED ON NEXT PAGE
EVOLOCUMAB

SAFETY (CONTINUED)
Repatha has not been studied in human pregnancy and lactation studies. Based on the human data from other human monoclonal antibodies, Repatha is unlikely to cross the placenta in the first trimester; however, it may cross the placenta in increasing amounts in the second and third trimester. Primate studies reveal no effects on pregnancy, embryo-fetal organ development, or postnatal development when evolocumab was administered at doses up to 12 times the maximum human dose. There is no information regarding the presence of Repatha 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. Repatha has been studied in a total of 14 adolescents with HoFH. Efficacy and safety of Repatha in adolescent patients with HoFH appears to be similar to that for adults with HoFH. The safety and efficacy of Repatha have not been established for patients younger than 13 years old or for pediatric patients without HoFH.

DOSAGE
For patients with primary hyperlipidemia with established clinical atherosclerotic CVD or HeFH, the recommended dose for Repatha is 140mg every 2 weeks or 420mg once monthly given by subcutaneous injection in the abdomen, thigh or upper arm. For patients with HoFH the dose is 420mg once monthly. At this time the 420mg pen or syringe dosage form is unavailable, so patients must administer 3 injections of 140mg dose consecutively within 30 minutes.

For patients with HoFH, measure LDL cholesterol levels within 4 to 8 weeks of initiating Repatha, to assess response. Response to PCSK9 inhibitor therapy in this population is dependent on the degree of LDL receptor function (patients with two LDL-receptor negative alleles did not respond to Repatha in clinical trials).

CONTINUED ON NEXT PAGE
EVLOCUMAB

REFERENCES


<table>
<thead>
<tr>
<th>Library</th>
<th>Commercial</th>
<th>NSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Created: 08/15
Effective: 01/01/16 Client Approval: 11/15