Commercial/Healthcare Exchange PA Criteria

Effective: May 4, 2016

Prior Authorization: Repatha

Products Affected: Repatha (evolocumab) Subcutaneous Solution

Medication Description:

Evolocumab (Repatha) is a human monoclonal IgG2 directed against human proprotein convertase subtilisin kexin 9 (PCSK9). Evolocumab binds to PCSK9 and inhibits circulating PCSK9 from binding to the low-density lipoprotein (LDL) receptor (LDLR), preventing PCSK9-mediated LDLR degradation and permitting LDLR to recycle back to the liver cell surface. By inhibiting the binding of PCSK9 to LDLR, evolocumab increases the number of LDLRs available to clear LDL from the blood, thereby lowering LDL-C levels.

Covered Uses:

1. **Established cardiovascular (CV) disease**, in adults to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization.
2. **Primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH])**, in adults as an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies to reduce LDL-C.
3. **HeFH, in pediatric patients ≥ 10 years of age**, as an adjunct to diet and other LDL-C lowering therapies.
4. **Homozygous familial hypercholesterolemia (HoFH)**, as an adjunct to diet and other low-density lipoprotein (LDL)-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients ≥ 10 years of age and older, to reduce LDL-C.

Exclusion Criteria:

Repatha has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions.

1. Concurrent use of Repatha with Praluent (alirocumab injection for SC use), Juxtapid (lomitapide capsules) or Leqvio (inclisiran subcutaneous injection. Praluent is another PCSK9 inhibitor and should not be used with Repatha. Juxtapid and Leqvio are agents indicated as an adjunct to lipid-lowering medications and diet to modify lipid parameters (e.g., reduce LDL-C levels) in patients with HoFH. The efficacy and safety of using Praluent, Juxtapid and Leqvio in combination with Repatha have not been established.

Required Medical Information

1. Diagnosis
2. Current LDL-C (within the past 90 days)
3. Previous trial of a high dose statin (i.e., atorvastatin 40mg; rosuvastatin 20mg)
4. Confirmation that a medication reconciliation has been performed, by the prescriber, to identify any potential drug interactions that could cause elevated statin levels

Age Restrictions:

1. **Hyperlipidemia in Patients with Clinical Atherosclerotic Cardiovascular Disease (ASCVD)**
   - The patient is aged ≥ 18 years
2. **Heterozygous Familial Hypercholesterolemia [HeFH]**

- The patient is aged ≥ 10 years

3. **Homozygous Familial Hypercholesterolemia [HoFH]**
   - The patient is aged ≥ 10 years
4. **Primary hypercholesterolemia**
   - The patient is aged ≥ 18 years

Prescriber Restrictions: Prescribed by, or in consultation with, a cardiologist, endocrinologist, or a physician who focuses in the treatment of CV risk management and/or lipid disorders.

Coverage Duration:

- Initial Prior Authorization: 12 weeks
- Continuation of Therapy: 12 months

Other Criteria:

1. **Atherosclerotic Cardiovascular Disease***

   Approve Repatha if the patient meets the following criteria (A, B, C, **AND** D):

   A. The patient is aged ≥ 18 years; **AND**

   B. The patient meets the following conditions or diagnosis (i, ii, iii, iv **OR** v)

   i. The patient has had a previous myocardial infarction (MI) or has a history of an acute coronary syndrome (ACS) **OR**

   ii. The patient has a diagnosis of angina (stable or unstable) **OR**

   iii. The patient has a past history of stroke or transient ischemic attack (TIA) **OR**

   iv. The patient has peripheral arterial disease (PAD) **OR**

   v. The patient has undergone a coronary or other arterial revascularization procedure in the past **AND**
   Note: Examples include coronary artery bypass graft [CABG], percutaneous coronary intervention [PCI], angioplasty, coronary stent procedure)

   C. The patient meets one of the following criteria (i **OR** ii):

   i. The patient meets both of the following (a **AND** b)

   a. The patient has tried at least ONE (1) high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily or rosuvastatin ≥ 20 mg daily) FOR ≥ 8continuous weeks **AND**

   b. The LDL-C level remains ≥ 70 mg/dL **OR**

   ii. The patient has been determined to be statin intolerant by meeting one of the following criteria (a **OR** b):

   a. The patient experienced statin-related rhabdomyolysis **OR**
   Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]);

   b. Patient meets all of the following (1, 2, **AND** 3)

   1. The patient experienced skeletal-related muscle symptoms **AND** (e.g., myopathy [muscle weakness] or myalgia [muscle aches, soreness, stiffness, or tenderness])
   2. The skeletal-related muscle symptoms (e.g., myopathy or myalgia) occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) **AND**
   3. When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms (e.g., myopathy,

myalgia) resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); **AND**

D. Repatha is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders.

2. <u>Heterozygous Familial Hypercholesterolemia [HeFH].</u> *

Approve Repatha if the patient meets the following criteria (A, B, C **AND** D):

A. The patient is aged ≥ 10 years; **AND**

B. The patient meets the following criteria (i, ii **OR** iii):

i. Patient has an untreated low-density lipoprotein cholesterol (LDL-C) ≥ 190 mg/dL (prior to treatment with antihyperlipidemic agents); **OR**

ii. Patient has genetic confirmation of heterozygous familial hypercholesterolemia by mutations in the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9, or low-density lipoprotein receptor adaptor protein 1 gene; **OR**

iii. Patient has been diagnosed with heterozygous familial hypercholesterolemia by meeting one of the following diagnostic criteria thresholds (a **OR** b):

a. Patient meets both of the following (1 **AND** 2)

1. Prescriber used the Dutch Lipid Network criteria to diagnose HeFH; **AND**

2. Patient had a score > 5; **OR**

b. Patient meets both of the following (1 **AND** 2)

1. Prescriber used the Simon Broome criteria to diagnose heterozygous familial hypercholesterolemia; **AND**

2. Patient met the threshold for "definite" or "possible (or probable)" familial hypercholesterolemia; **AND**

C. The patient meets one of the following criteria (i **<u>OR</u>** ii):

i. The patient meets both of the following criteria (a **AND** b)

a. The patient has tried at least ONE (1) high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily or rosuvastatin ≥ 20 mg daily) for ≥ 8continuous weeks **AND**

b. The LDL-C level remains ≥ 70 mg/dL **OR**

ii. The patient has been determined to be statin intolerant by meeting one of the following criteria (a **<u>OR</u>** b):

a. The patient experienced statin-related rhabdomyolysis **OR**
Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]);

b. The Patient meets all of the following (1, 2 **AND** 3)

1. Patient experienced skeletal-related muscle symptoms; **AND**
<u>Note</u>: *Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).*

2. The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); **AND**

3. When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); **AND**
<u>Note</u>: *Examples of skeletal-related muscle symptoms include myopathy and myalgia.*

D. Repatha is prescribed by, or in consultation with, a cardiologist; an endocrinologist; or a physician who focuses in the treatment of cardiovascular (CV) risk management and/or lipid disorders

3. Homozygous Familial Hypercholesterolemia [HoFH] *

Approve Repatha if the patient meets the following criteria (A, B, C, **AND** D):

A. The patient is aged ≥ 10 years; **AND**

B. The patient meets the following criteria (i, ii **OR** iii):

i. Patient has genetic confirmation of two mutant alleles at the low-density lipoprotein receptor, apolipoprotein B, proprotein convertase subtilisin kexin type 9 (PCSK9), or low-density lipoprotein receptor adaptor protein 1 gene locus; **OR**

ii. Patient has an untreated low-density lipoprotein cholesterol (LDL-C) level > 500 mg/dL AND meets one of the following (a **OR** b): Note: Untreated refers to therapy with any antihyperlipidemic agent.

a. Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; **OR**

Note: Clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas, or xanthelasma.

b. Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; **OR**

Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C level ≥ 190 mg/dL and/or an untreated total cholesterol level > 250 mg/dL.

iii. Patient has a treated LDL-C level ≥ 300 mg/dL AND meets one of the following (a **OR** b)

Note: Treated refers to after therapy with at least one antihyperlipidemic agent. Some examples of antihyperlipidemic agents include statins (e.g., atorvastatin, rosuvastatin, lovastatin, simvastatin, pravastatin), ezetimibe, a PCSK9 inhibitor (e.g., Praluent [alirocumab subcutaneous injection]), Evkeeza (evinacumab-dgnb intravenous infusion), or Juxtapid (lomitapide capsules)

a. Patient had clinical manifestations of homozygous familial hypercholesterolemia before 10 years of age; **OR**

Note: Examples of clinical manifestations of homozygous familial hypercholesterolemia are cutaneous xanthomas, tendon xanthomas, arcus cornea, tuberous xanthomas or xanthelasma.

b. Both parents of the patient had untreated LDL-C levels or total cholesterol levels consistent with heterozygous familial hypercholesterolemia; **AND**

Note: An example of heterozygous familial hypercholesterolemia in both parents would be if both had an untreated LDL-C ≥ 190 mg/dL and/or an untreated total cholesterol > 250 mg/dL.

C. Patient meets one of the following criteria (i **OR** ii):

i. Patient meets both of the following (a **AND** b):

a. Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]) for ≥ 8 continuous weeks; **AND**

b. LDL-C level after this treatment remains ≥ 70 mg/dL; **OR**

ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a **OR** b):

a. Patient experienced statin-related rhabdomyolysis; **OR**

Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]);

b. Patient meets all of the following criteria (1, 2 **AND** 3)

1. Patient experienced skeletal-related muscle symptoms; **AND** Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
2. The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); **AND**

3. When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); **AND**
   Note: Examples of skeletal-related muscle symptoms include myopathy or myalgia.

D. Prescribed by, or in consultation with, a cardiologist, endocrinologist, or a physician who focuses in the treatment of CV risk management and/or lipid disorders.

4. Primary Hyperlipidemia. *

Approve Repatha if the patient meets the following criteria (A, B, C, **AND** D):
Note: This is not associated with atherosclerotic cardiovascular disease (ASCVD), heterozygous familial hypercholesterolemia (HeFH), or homozygous familial hypercholesterolemia (HoFH) and may be referred to as combined hyperlipidemia, hypercholesterolemia (pure, primary), dyslipidemia, or increased/elevated low-density lipoprotein cholesterol (LDL-C) levels.

A. The patient is aged ≥ 18 years; **AND**
B. Patient has a coronary artery calcium or calcification score ≥ 300 Agatston units; **AND**
C. Patient meets one of the following criteria (i **OR** ii):
   i. Patient meets all of the following criteria (a, b, and c):
      a. Patient has tried one high-intensity statin therapy (i.e., atorvastatin ≥ 40 mg daily; rosuvastatin ≥ 20 mg daily [as a single-entity or as a combination product]); **AND**
      b. Patient has tried one high-intensity statin therapy above along with ezetimibe (as a single-entity or as a combination product) for ≥ 8 continuous weeks; **AND**
      c. LDL-C level after this treatment regimen remains ≥ 100 mg/dL; **OR**
   ii. Patient has been determined to be statin intolerant by meeting one of the following criteria (a **OR** b):
      a. Patient experienced statin-related rhabdomyolysis; **OR**
         Note: Rhabdomyolysis is statin-induced muscle breakdown that is associated with markedly elevated creatine kinase levels (at least 10 times the upper limit of normal), along with evidence of end organ damage which can include signs of acute renal injury (noted by substantial increases in serum creatinine [Scr] levels [a ≥ 0.5 mg/dL increase in Scr or doubling of the Scr] and/or myoglobinuria [myoglobin present in urine]); **OR**
      b. Patient meets all of the following (1, 2, **AND** 3):
         1. Patient experienced skeletal-related muscle symptoms; **AND**
            Note: Examples of skeletal-related muscle symptoms include myopathy (muscle weakness) or myalgia (muscle aches, soreness, stiffness, or tenderness).
         2. The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products); **AND**
         3. When receiving separate trials of both atorvastatin and rosuvastatin (as single-entity or as combination products) the skeletal-related muscle symptoms resolved upon discontinuation of each respective statin therapy (atorvastatin and rosuvastatin); **AND**
            Note: Examples of skeletal-related muscle symptoms include myopathy or myalgia.
D. Medication is prescribed by or in consultation with a cardiologist, an endocrinologist, or a physician who focuses in the treatment of cardiovascular risk management and/or lipid disorders.

Note:
* A patient may have a diagnoses that pertain to more than one FDA-approved indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia or homozygous familial hypercholesterolemia may have had a clinical ASCVD event, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).

Renewal Criteria:

1. **Hyperlipidemia in Patients with Clinical Atherosclerotic Cardiovascular Disease (ASCVD)**
   Approve if according to the prescribing physician, the patient has experienced a response to therapy.
2. **Heterozygous Familial Hypercholesterolemia [HeFH]**
   Approve if according to the prescribing physician, the patient has experienced a response to therapy.
3. **Homozygous Familial Hypercholesterolemia [HoFH]**
   Approve if according to the prescribing physician, the patient has experienced a response to therapy.
4. **Primary hypercholesterolemia**
   Approve if according to the prescribing physician, the patient has experienced a response to therapy.

References:

1. Repatha [package insert]. Thousand Oaks, CA; Amgen; August 2015.
2. Robinson et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: the LAPLACE-2 randomized clinical trial. JAMA. 2014 May 14;311(18):1870-82.
3. Blom et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. N Engl J Med. 2014 May 8;370(19):1809-19.
4. Raal et al. PCSK9 inhibition with evolocumab (AMG 145) in heterozygous familial hypercholesterolemia (RUTHERFORD-2): a randomized, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):331-40.
5. Raal et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolemia (TESLA Part B): a randomized, double-blind, placebo-controlled trial. Lancet. 2015 Jan 24;385(9965):341-50.
6. FDA Briefing Information: Evolocumab. The Endocrinologic and Metabolic Drugs Advisory Committee Meeting. FDA Center for Drug Evaluation and Research.2015 June 10. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM450072.pdf. Accessed August 31, 2015.
7. Stone NJ, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation, 2014; 129(25 Suppl 2): S1-45.
8. Jacobson et al. National Lipid Association recommendations for patient-centered management of dyslipidemia: Part 1 – executive summary. Journal of Clinical Lipidology. 2014. Available at: http://www.sciencedirect.com/science/article/pii/S1933287414002748. Accessed August 31, 2015
9. FDA approves Repatha to treat certain patients with high cholesterol. FDA News Release. 27 August 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm460082.htm

Policy Revision history

Rev #	Type of Change	Summary of Change	Sections Affected	Date
1	New Policy	New Policy	All	01/13/2016
2	Clinical Update	Clarification of covered uses, renewal criteria removed	Covered Uses, Other criteria	03/01/2016
3	Additional criteria	Medication reconciliation requirement	Required Medical Information	12/12/2017
4	Update Criteria	Clinical criteria updated	Other Criteria	5/23/2018
5	Update Criteria	New Indication	Other Criteria, Age Restriction, Covered Uses	07/20/2018
6	Policy	ConnectiCare adoption of EH Policy	All	7/25/18
7	Update	Updated clinical criteria to require the use of one high-intensity statin	Required Medical Information Other Criteria	2/10/2020

8	Update	Updated age restriction for Homozygous Familial Hypercholesterolemia [HoFH] AND Heterozygous Familial Hypercholesterolemia (HeFH) to 10 years of age and older to align with FDA's new age approval Removed: "E) If able to tolerate statins, the patient continues to receive the maximum tolerated dose of a statin while receiving Repatha therapy" for 2. Heterozygous Familial Hypercholesterolemia (HeFH) and 4. Primary Hypercholesterolemia	Age Restrictions Other Criteria	12/17/2021
9	Update	Removed: "E) If able to tolerate statins, the patient continues to receive the maximum tolerated dose of a statin while receiving Repatha therapy" for 1. ASCVD and 3. HoFH Removed renewal criteria point "continued adherence to maximally tolerated statin dose" for all indications.	Other Criteria Renewal Criteria	12/29/2021

10	Update	Update covered uses to include; **Established** cardiovascular (CV) disease, in adults to reduce the risk of myocardial infarction (MI), stroke, and coronary revascularization. Primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]), in adults as an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies to reduce LDL-C. HeFH, in pediatric patients ≥ 10 years of age, as an adjunct to diet and other LDL-C lowering therapies. Homozygous familial hypercholesterolemia (HoFH), as an adjunct to diet and other low-density lipoprotein (LDL)-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients ≥ 10 years of age and older, to reduce LDL-C. Removal of Kynamro in exclusion criteria. Clarification of covered uses to mirror ESI criteria and decrease high intensity statin therapy of Atorvastatin 80mg to 40mg and Rosuvastatin 40mg to 20mg. Added **Note:** * A patient may have a diagnoses that pertain to more than one FDA-approved indication, therefore, consider review under different approval conditions, if applicable (e.g., a patient with heterozygous familial hypercholesterolemia or homozygous familial hypercholesterolemia may have had a clinical ASCVD event, a patient with primary hyperlipidemia may have heterozygous familial hypercholesterolemia).	Medication Description Exclusion criteria Covered uses Note	5/17/2022

11	Update	Renewal Criteria: removed " Renewal Criteria: 1. Hyperlipidemia in Patients with Clinical Atherosclerotic Cardiovascular Disease (ASCVD) - Lipid panel showing > 40% reduction in LDL-C from baseline. 2. Heterozygous Familial Hypercholesterolemia [HeFH] - Lipid panel showing > 40% reduction in LDL-C from baseline. 3. Homozygous Familial Hypercholesterolemia [HoFH] - Lipid panel showing > 20% reduction in LDL-C from baseline. 4. Primary hypercholesterolemia - Lipid panel showing > 40% reduction in LDL-C from baseline." Added "1. Hyperlipidemia in Patients with Clinical Atherosclerotic Cardiovascular Disease (ASCVD) Approve if according to the prescribing physician, the patient has experienced a response to therapy. 2. Heterozygous Familial Hypercholesterolemia [HeFH] Approve if according to the prescribing physician, the patient has experienced a response to therapy. 3. Homozygous Familial Hypercholesterolemia [HoFH] Approve if according to the prescribing physician, the patient has experienced a response to therapy. 4.Primary hypercholesterolemia Approve if according to the prescribing physician, the patient has experienced a response to therapy"	Renewal criteria	5/18/2023