

From The Medical Letter on Drugs and Therapeutics

# Evolocumab (Repatha)—A Second PCSK9 Inhibitor to Lower LDL-Cholesterol

**Evolocumab (Repatha - Amgen)**, a subcutaneously injected PCSK9 inhibitor, has been approved by the FDA as an adjunct to diet and maximally tolerated statin therapy for adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-cholesterol (LDL-C) (Table 1). It was also approved as an adjunct to diet and other LDL-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C. Evolocumab is the second PCSK9 inhibitor to be approved in the US; alirocumab (Praluent) was approved earlier (Table 2).<sup>1</sup>

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### Mechanism of Action

PCSK9 (proprotein convertase subtilisin kexin type 9) binding to LDL receptors on hepatocytes promotes receptor degradation, prevents LDL-C clearance from blood, and increases serum concentrations of LDL-C. Evolocumab is a human IgG<sub>2</sub> monoclonal antibody that targets PCSK9, prevents it from binding to LDL receptors, and increases hepatic uptake of LDL-C.

### Clinical Studies

Results of some clinical trials of evolocumab are summarized in Table 3.<sup>2-6</sup>

A prespecified exploratory analysis of the OSLER-1 and -2 trials found that after one year, the Kaplan-Meier estimated percentages

Table 1. Pharmacology

Class	PCSK9 inhibitor
Formulation	140 mg/mL preservative-free solution in single-use prefilled syringe or autoinjector
Route	Subcutaneous injection
Tmax	3-4 days
Metabolism	Probably degradation to small peptides and amino acids
Elimination	Low concentrations: primarily saturable binding to PCSK9 Higher concentrations: primarily nonsaturable proteolysis
Half-life	11-17 days

Table 2. PCSK9 Inhibitors for Hypercholesterolemia

Drug	Formulations	Usual Adult Dosage	Cost <sup>a</sup>
Alirocumab – Praluent (Sanofi/Regeneron)	75, 150 mg/mL single-use pens, prefilled syringes	Initial: 75 mg SC q2 wks Max: 150 mg SC q2 wks	13 440.00
Evolocumab – Repatha (Amgen)	140 mg/mL single-use autoinjectors, prefilled syringes	Initial: 140 mg SC q2 wks or 420 mg SC once/month <sup>b</sup> Max: 140 mg SC q2 wks or 420 mg SC once/month <sup>b</sup>	13 015.40

<sup>a</sup> Approximate WAC for one year's treatment at the lowest initial dose. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource® Monthly. September 5, 2015. Reprinted with

Pronunciation Key	
Evolocumab: e' voe lok' ue mab	Repatha: ri pa' tha

of patients having a cardiovascular event were significantly lower among those receiving evolocumab than those receiving standard treatment alone (0.95% vs 2.18%).<sup>2</sup> A more definitive study to evaluate the effect of evolocumab on cardiovascular outcomes (FOURIER) is underway.

### Adverse Effects

The most common adverse effects reported in clinical trials with evolocumab included nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection-site reactions.

A meta-analysis of 12 randomized, controlled trials found that there were no significant differences in adverse events between evolocumab, ezetimibe, and placebo.<sup>7</sup> Neurocognitive events were reported in <1% of patients receiving evolocumab, but more often than in those receiving placebo.

### Pregnancy

Evolocumab has not been studied in pregnant women. Monoclonal antibodies are unlikely to cross the placenta in the first trimester, but may do so subsequently. Animal studies found that evolocumab had no adverse effects on the fetus.

### Dosage and Administration

The recommended starting dosage of evolocumab is 140 mg injected subcutaneously once every 2 weeks or 420 mg (three 140-mg injections within 30 minutes) once monthly in patients with HeFH or clinical atherosclerotic cardiovascular disease, or 420 mg once monthly in patients with HoFH. The drug should be injected into the abdomen, thigh, or upper arm; the injection site should be rotated with each use. If a dose is missed, it should be administered only if the next dose is scheduled to be given at least 7 days later. LDL-C levels should be measured 4-8 weeks after starting evolocumab in patients with HoFH.

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<sup>b</sup> Dosage for patients with heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic CVD. Dosage for patients with homozygous familial hypercholesterolemia (HoFH) is 420 mg SC once monthly.

Table 3. Some Evolocumab Clinical Trials

Trial	Population	Treatment Arms	Mean LDL-C Change (Placebo-Corrected)
OSLER-1 and -2 (n = 4465) [52 weeks] <sup>a</sup>	Patients with various degrees of high LDL-C	Evolocumab 140 mg q2 wks <sup>b</sup> Evolocumab 420 mg q4 wks <sup>b</sup> Standard treatment alone <sup>c</sup>	-60.9% <sup>d</sup>
DESCARTES (n = 901) [52 weeks] <sup>e</sup>	LDL-C ≥75 mg/dL with diet alone, diet plus statin therapy, or statin therapy with or without ezetimibe	Evolocumab 420 mg q4 wks Placebo	-57.0%
MENDEL-2 (n = 614) [12 weeks] <sup>f</sup>	Low CV risk patients with LDL-C ≥100 and <190 mg/dL receiving no background therapy	Evolocumab 140 mg q2 wks Evolocumab 420 mg q4 wks Ezetimibe once/d Placebo	-57.1% -54.8% -17.9% <sup>g</sup>
RUTHERFORD-2 (n = 331) [12 weeks] <sup>h</sup>	HeFH on stable lipid-lowering therapy	Evolocumab 140 mg q2 wks Evolocumab 420 mg q4 wks Placebo	-59.2% -61.3%
TESLA Part B (n = 49) [12 weeks] <sup>i</sup>	HoFH on stable lipid-lowering therapy	Evolocumab 420 mg q4 wks Placebo	-30.9%

Abbreviations: CV, cardiovascular; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL-C, LDL-cholesterol.

<sup>a</sup> MS Sabatine et al. *N Engl J Med* 2015; 372:1500.

<sup>b</sup> In addition to standard treatment.

<sup>c</sup> Standard treatment was based on local guidelines for treatment of LDL-C.

<sup>d</sup> LDL-C change at 12 weeks for both doses of evolocumab relative to standard of care alone.

<sup>e</sup> DJ Blom et al. *N Engl J Med* 2014; 370:1809.

<sup>f</sup> MJ Koren et al. *J Am Coll Cardiol* 2014; 63:2531.

<sup>g</sup> Mean LDL-C change for patients also receiving biweekly and once monthly placebo injections, respectively.

<sup>h</sup> FJ Raal et al. *Lancet* 2015; 385:331.

<sup>i</sup> FJ Raal et al. *Lancet* 2015; 385:341.

Evolocumab should be stored in the refrigerator, and warmed to room temperature for at least 30 minutes before injection. It can also be stored at room temperature, but must be used within 30 days.

## Conclusion

The second FDA-approved PCSK9 inhibitor evolocumab (Repatha) appears to be similar in efficacy and safety to alirocumab (Praluent),

but no comparative studies are available. Given by subcutaneous injection every 2 weeks or once monthly, evolocumab can further lower LDL-cholesterol levels by about 60% in patients at high risk for atherosclerotic cardiovascular disease already taking maximal statin therapy. Its effect on cardiovascular outcomes remains to be established. The long-term efficacy and safety of both evolocumab and alirocumab are unknown, and they are expensive.

## ARTICLE INFORMATION

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