

**EVOLOCUMAB injection (Repatha SureClick® ▼)  
for reduction of cardiovascular risk in adults  
with established atherosclerotic cardiovascular disease**

The Pan Mersey Area Prescribing Committee does not recommend the prescribing of EVOLOCUMAB injection (Repatha SureClick® ▼) for reduction of cardiovascular risk in adults with established atherosclerotic cardiovascular disease

**BLACK**

Evolocumab is licensed in adults with established atherosclerotic cardiovascular (CV) disease (myocardial infarction, stroke or peripheral arterial disease) to reduce CV risk by lowering LDL-cholesterol levels, as an adjunct to correction of other risk factors:

- > in combination with the maximum tolerated dose of a statin, with or without other lipid-lowering therapies or,
- > alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.<sup>1</sup>

**Evolocumab is also licensed for treating primary hypercholesterolaemia and mixed dyslipidaemia.<sup>1</sup> Pan Mersey APC supports use for this indication only in strict accordance with NICE [TA394](#).**

**The Pan Mersey APC does not recommend evolocumab for the reduction of CV risk in adults with established atherosclerotic CV disease for the following reasons:**

- > The results from the pivotal study (FOURIER)<sup>2</sup> showed that evolocumab was more effective at reducing LDL-cholesterol levels than placebo and that CV events were reduced with evolocumab vs placebo. However, no observed effect on CV mortality was demonstrated.
- > In the FOURIER study, patients from Europe derived a lesser benefit from evolocumab on the key secondary composite end point of CV death, myocardial infarction (MI), or stroke than patients from North America.
- > An assessment of the cost-effectiveness of evolocumab for reducing CV events in US patients with atherosclerotic CV disease found that in order for evolocumab to be cost effective with an ICER of \$100,193 (£75,670), the annual net price would have to be \$10,311 (£7,787).<sup>3</sup> As NICE generally considers interventions with an ICER of less than £20,000 per QALY gained to be cost-effective<sup>4</sup>, evolocumab at the current UK annual cost (£4,082.40) is unlikely to meet the NICE threshold. Therefore, the cost-effectiveness of evolocumab for this extended population could not be assured.
- > The license extension is extremely broad, and therefore the anticipated patient numbers could be very large. At present a cohort of patients has not been identified for this extended indication where evolocumab could be considered to be cost-effective.

**Note:** Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

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### Effectiveness<sup>2</sup>

Evolocumab is a PCSK9 inhibitor. Evolocumab binds selectively to PCSK9 and prevents circulating PCSK9 from binding to the LDL receptor on the liver cell surface, thus preventing PCSK9-mediated LDL receptor degradation. Increasing liver LDL receptor levels results in associated reductions in serum LDL-cholesterol.<sup>1</sup>

The pivotal study (FOURIER) was a large 27,564 patient, multi region randomised, double-blind, placebo-controlled trial. The median LDL-cholesterol level at baseline was 2.4 mmol/L. At 48 weeks, the least-squares mean percentage reduction in LDL-cholesterol levels with evolocumab, compared with placebo, was 59% (95% confidence interval [CI], 58 to 60;  $P < 0.001$ ), for a mean absolute reduction of 1.45 mmol/L (95% CI, 1.43 to 1.47), to a median of 0.78 mmol/L [interquartile range, 0.49 to 1.2]).

The primary efficacy end point (composite of CV death, MI, stroke, hospitalisation for unstable angina, or coronary revascularisation) occurred in 1344 patients (9.8%) in the evolocumab group vs 1563 patients (11.3%) in the placebo group (hazard ratio, 0.85; 95% CI, 0.79 to 0.92;  $P < 0.001$ ). The key secondary end point (composite of CV death, MI, or stroke) occurred in 816 patients (5.9%) in the evolocumab group vs 1013 patients (7.4%) in the placebo group (hazard ratio, 0.80; 95% CI, 0.73 to 0.88;  $P < 0.001$ ).

Risk reduction with regard to the primary end point was 12% in the first year and 19% beyond the first year. The key secondary end point risk reduction was 16% in the first year and 25% beyond the first year.

Evolocumab had no observed effect on CV mortality.

### Cost<sup>5</sup>

Drug	Example regimen	Pack cost (NHS List price)	Cost per patient / per year (ex VAT)
Evolocumab 140mg/1ml pen	1 x 140mg s/c injection every two weeks	£340.20 (2 pens)	£4,082.40
Atorvastatin 80mg tablets	80mg OD	£1.65 (28 tablets)	£19.80
Ezetimibe 10mg tablets	10mg OD	£2.17 (28 tablets)	£26.04

This table does not imply therapeutic equivalence of drugs or doses.

Expected patient numbers are unknown but likely to be large due to the broad nature of the license extension indication.

### Safety<sup>1</sup>

The most commonly reported adverse reactions during pivotal trials, at the recommended doses, were nasopharyngitis (7.4%), upper respiratory tract infection (4.6%), back pain (4.4%), arthralgia (3.9%), influenza (3.2%), and injection site reactions (2.2%).

In the FOURIER study there was no significant difference between the study groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were more common with evolocumab (2.1% vs. 1.6%).<sup>2</sup>

The needle cover of the pre-filled pen is made from dry natural rubber (a derivative of latex), which may cause allergic reactions.

### Pregnancy

There are no or limited amount of data from the use of evolocumab in pregnant women. Evolocumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with evolocumab.

### Breastfeeding

It is unknown whether evolocumab is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or discontinue/abstain from evolocumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Refer to [SPC](#) for full details.

### Patient factors<sup>1</sup>

#### Patients with renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Repatha should be used with caution in patients with severe renal impairment (defined as eGFR  $< 30$  mL/min/1.73 m<sup>2</sup>).

#### Patients with hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment. In patients with moderate hepatic impairment, a reduction in total evolocumab exposure was observed that may lead to a reduced effect on LDL-cholesterol reduction. Therefore, close monitoring may be warranted in these patients. Repatha should be used with caution in patients with severe hepatic impairment (Child-Pugh C).

#### Elderly patients (age $\geq 65$ years)

No dose adjustment is necessary.

### Prescribing and implementation information

Evolocumab is not recommended for CV risk reduction in adults with established atherosclerotic CV disease. Prescribers should continue to follow current national guidance for lipid modification:

- > [NICE CG181](#): Cardiovascular disease: risk assessment and reduction, including lipid modification (last updated September 2016).

## SUPPORTING INFORMATION

### References

1. Amgen Ltd. Summary of Product Characteristics, [Repatha SureClick](#). May 2018. Accessed 01 April 2019.
2. Sabatine MS, Giugliano RP, Keech AC et al., Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease, N Engl J Med 2017;376:1713-22. Accessed online 01 April 2019: <https://www.nejm.org/doi/pdf/10.1056/NEJMoa1615664>
3. Fonarow GC, Keech AC, Pedersen PR, et al., Cost-effectiveness of Evolocumab Therapy for Reducing Cardiovascular Events in Patients With Atherosclerotic Cardiovascular Disease, JAMA Cardiol. 2017;2(10):1069-1078. Accessed online 01 March 2019: <https://jamanetwork.com/journals/jamacardiology/fullarticle/2649273>
4. National Institute for Health and Care Excellence. [The guidelines manual](#) Process and methods [PMG6], 30 November 2012. Accessed 01 March 2019
5. NHSBA Dictionary of Medicine and Devices. ([dm+d Browser](#)). Accessed 01 April 2019.