Northern Treatment Advisory Group

Northern (NHS) Treatment Advisory Group

Treatment Appraisal: Decision Summary

Date	**24th November 2015**
Appraisal & Details	**Evolocumab (Repatha®▼, Amgen) for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia.** The Northern (NHS) Treatment Advisory Group considered an appraisal of evolocumab, monoclonal anti-PCSK9 antibody, licensed for the treatment of adults aged 18 and over with primary hypercholesterolemia (heterozygous familial or non-familial) or mixed dyslipidaemia, as an adjunct to diet: • in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of the statin or, • Alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. It acts by reducing circulating levels of low-density lipoprotein cholesterol (LDL-C). Treatment for homozygous FH is commissioned by NHS England, and is not covered by this recommendation.
Recommendation	**The Northern (NHS) Treatment Advisory Group does not recommend the use of evolocumab for the above indication.** The evidence for the clinical efficacy and safety of evolocumab is limited, with the majority of the evidence for efficacy derived from five phase III trials, each lasting 12 weeks. Only one phase III trial lasted 52 weeks. There is currently insufficient data on the effect of evolocumab on CV morbidity and mortality and therefore questions remain around risk reduction, cost effectiveness and affordability of treatment. The group also considered the use of evolocumab for a specific subgroup of patients who would otherwise be eligible for apheresis, as advised by specialists however there is insufficient information on efficacy of evolocumab in this patient population. The group was concerned about the level of clinical benefit versus cost of evolocumab in this patient group. It was noted that the current cohort of patients were not receiving apheresis and reasons for this should be explored first. Evolocumab may be suitable for those patients with heterozygous familial hypercholesterolemia (HeFH) who are at very high risk however it was felt that these patients should be managed on a case by case basis. The group is aware that a NICE technology appraisal review is currently underway and agreed that NICE is best place to assess cost effectiveness due to the current gaps in the data and will await this guidance.
Clinical evidence summary	Five published trials assess the efficacy of evolocumab for the reduction of LDL-C in various populations. Evolocumab produced greater reductions in LDL-C than either placebo or ezetimibe in all trials. Reductions were around 55-60% at the end of 12 weeks treatment, compared to typical reductions of

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	15-20% in the groups assigned to ezetimibe. LDL-C reductions in the 52 week DESCARTES trial were slightly lower than in the 12 weeks studies at 45-50%. The efficacy in the two weekly and monthly dosing groups was comparable at 12 weeks. Significant reductions in other lipid parameters were also observed. Whilst there are no head to head trials, evolocumab appears to result in slightly greater LDL-C reductions than alirocumab, but variances in the underlying populations studied may explain these relatively small differences. The effect of evolocumab on cardiovascular morbidity and mortality has not been established. Rates appear to be lower than in control groups, but the number of events collected in published trials was low. A 5 year cardiovascular outcomes trial is currently underway. The group noted that as highlighted in the draft NICE guidance on evolocumab that the ongoing FOURIER trial will test whether LDL-C is a valid surrogate for CV outcomes, which the ERG considered to be a key area of uncertainty in the current evidence.
Safety	The safety profile of evolocumab was comparable to the comparators. The most common AEs were nasopharyngitis, upper respiratory tract infection, headache and back pain. Rates of serious AEs and AEs leading to discontinuation were low. However the long-term safety of evolocumab remains to be established.
Patient Perspective	Hypercholesterolaemia is major risk factor for the development and progression of cardiovascular disease (CVD). Long-term exposure to significantly elevated LDL-C accelerates the development of atherosclerosis which can lead to angina, myocardial infarction and stroke, particularly in patients with HeFH. Untreated, men have a greater than 50% risk of coronary heart disease (CHD) by the age of 50 years, and women at least 30% by the age of 60 years. Evolocumab offers another treatment option for high risk patients; however it is given as a sub cutaneous injection which needs to be given either every two weeks or monthly. Patients can be taught how to self-administer the injection however the injection formulation may be off putting for some patients. The monthly regimen offers the advantage of less frequent dosing but increases the injection burden by requiring three injections to be given in quick succession. It is also questionable as to whether patients will be willing to comply with treatment in order to treat an asymptomatic risk factor.
Cost analysis summary	The pre-filled syringe costs £170.10 for a single 140 mg dose, while the pre-filled pen costs £340.20 for a pack of two single-use devices each containing a single 140 mg dose (all prices exclude VAT). Evolocumab is expensive at £4,400 to £6,100 per patient per year depending on dose compared to £342 for ezetimibe. The incremental cost of using evolocumab instead of ezetimibe is roughly £4,100 to £5,800 per patient per year. In cases where they are added to background therapy this cost will be additive.

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Financial impact PbR: excluded	Accurately estimating the numbers of patients who might be eligible for treatment with alirocumab within its licensed indication is difficult. NICE estimates that primary non-FH affects around 4 in 100 of the adult population, and primary HeFH affects around 1 in 500 people. NICE estimate that only around 2% of eligible patients are unable to take statins because of contraindications or intolerance. Therefore approximately 1,670 patients (64 per 100,000 population) could be eligible for treatment with evolocumab or ezetimibe. Of those patients who are able to tolerate statins, around 30% would be considered for an alternative statin or ezetimibe or evolocumab. Thus, approximately 24,555 patients (941 per 100,000 population) could be eligible for treatment with a statin in combination with evolocumab. However Specialists identified approximately 40 patients across the NTAG region with severe HeFH who may be eligible for treatment as well as a further 40 patients with non-FH but with progressive, symptomatic coronary heart disease and persistently high non-HDL-C. Based on treating 80 patients with evolocumab costs would be an around £352,000 across the NTAG region