Northern Treatment Advisory Group

Northern (NHS) Treatment Advisory Group

Treatment Appraisal: Decision Summary

Date	**24th November 2015**
Appraisal & Details	**Alirocumab (Praluent®▼, Sanofi) for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia.** The Northern (NHS) Treatment Advisory Group considered an appraisal of alirocumab, a monoclonal anti-PCSK9 antibody licensed for the treatment of primary hypercholesterolaemia (familial and non-familial) and mixed dyslipidaemia in adults as an adjunct to diet: • In combination with a statin or statin with other LMTs in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, • Alone or in combination with other LMTs 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).
Recommendation	**The Northern (NHS) Treatment Advisory Group does not recommend the use of alirocumab for the above indication.** The group noted that whilst phase III trials involving 5296 patients demonstrated a substantial reduction in the primary end point of LDL-C reduction after 24 weeks, there is currently insufficient data on the effect of alirocumab on CV morbidity and mortality and therefore questions remain around the level of risk reduction and therefore the cost effectiveness of treatment. The group also considered the use of alirocumab 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 alirocumab in this patient population. The group was concerned about the level of clinical benefit (i.e risk reduction) versus the high cost of alirocumab 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. Alirocumab 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	Across ten phase 3 trials evaluating patients with HeFH and non-FH at high and moderate CV risk, alirocumab demonstrated a substantial reduction in the primary endpoint of LDL-C reduction after 24 weeks. On top of standard care (maximally tolerated statin +/- other lipid modifying treatments), a reduction of 39% to 62% compared to placebo was observed. Compared with ezetimibe, a reduction of 30% was found on top of standard care, 24% to 36% on less than

	maximal statins, and 30% to 32% without statin background therapy. The primary endpoint analyses were supported by consistent changes in the secondary lipid profile endpoints across all studies. The effect of alirocumab on cardiovascular morbidity and mortality has not been established. None of the trials completed to date had mortality associated with CV events as a pre-specified primary outcome. 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 alirocumab was comparable to that of the control groups (placebo or ezetimibe). The most common treatment-emergent adverse events were nasopharyngitis, injection site reaction, upper respiratory tract infection, influenza, headache, myalgia, and arthralgia. The number of patients discontinuing treatment or experiencing serious adverse events was low. None of the safety concerns commonly associated with other LMTs, such as liver disorders, renal disorders, diabetes and musculoskeletal disorders, was evident with alirocumab treatment. However, the long-term safety of alirocumab 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. Alirocumab offers another treatment option for high risk patients; however it is given as a sub cutaneous injection which needs to be given every two weeks. Patients can be taught how to self-administer the injection however the injection formulation may be ‘off putting’ for some patients. 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	No published economic analyses on the use of alirocumab were identified although a NICE TA is underway. Both the alirocumab 75 mg/ml and the 150 mg/ml doses cost £168.00 for one single-use pen or syringe, and £336.00 for two (all prices exclude VAT). A patient access scheme may be available however without a guarantee of a price reduction for the total duration of treatment NTAG considered the list price only when making this recommendation. Alirocumab is relatively expensive at £4,360 per patient per year compared to £342 for ezetimibe. If alirocumab was used instead of ezetimibe the incremental cost would be £4,018 per patient per year. In some patients alirocumab may be used in addition to ezetimibe, and therefore the costs would 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 alirocumab or ezetimibe. Of those patients who are able to tolerate statins, around 30% would be considered for an alternative statin, or alirocumab or ezetimibe. Thus, approximately 24,555 patients (941 per 100,000 population) could be eligible for treatment with a statin in combination with alirocumab. 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 alirocumab costs would be an around £350,000 across the NTAG region.