Cost-effectiveness of alirocumab (Praluent®) for the hypercholesterolemia

The NCPE has issued a recommendation regarding the cost-effectiveness of alirocumab (Praluent®). Following NCPE assessment of the applicant's submission, alirocumab (Praluent®) is not considered cost-effective for the treatment of hypercholesterolemia and therefore is not recommended for reimbursement.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Sanofi) economic dossier on the cost effectiveness of alirocumab (Praluent®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **June 2017**

Summary

In January 2016, Sanofi submitted a dossier to examine the cost effectiveness of alirocumab under the High Tech Drug Scheme. Alirocumab is a monoclonal antibody that inhibits proprotein convertase subtilisin-kexin type 9 (PCSK9) and is licensed in combination with maximum tolerated statin therapy for patients unable to reach LDL-C goals. The effect of alirocumab on cardiovascular morbidity and mortality has yet to be determined. It is administered as a subcutaneous injection at a dose of 75mg or 150mg every two weeks (Q2W) or 300mg once monthly (QM).

1. Comparative effectiveness of alirocumab

Alirocumab's phase III clinical development program (ODYSSEY) consists of a series of double-blind, multicentre randomised controlled trials. Ten trials which formed the basis for the initial marketing authorisation were presented by the applicant. Three trials specifically examined alirocumab's efficacy in patients with heterozygous familial hypercholesterolemia (HeFH). The majority of patients in the remaining trials were classified as high CV risk. In two trials the starting dose administered to all patients was 150mg every two weeks (Q2W) – the highest available dose. However the majority of studies evaluated an alirocumab up titration regimen where patients initiated therapy on alirocumab 75mg Q2W. Patients were up titrated to 150mg Q2W at week 12 if the pre-defined LDL-C target was not previously reached. The 300mg (QM) dosing regimen was not analysed as it was not licensed at the time of submission.

Comparators in the trials included placebo, ezetimibe or statin up titration. The treatment period of the trials ranged from 24 weeks to 104 weeks. Across all trials the primary endpoint was the difference in least squares (LS) mean percentage change in calculated LDL-C from baseline compared to the relevant comparator at 24 weeks. Depending on the patient population and the dose of alirocumab used the least squares mean reduction in LDL-C varied from 39.1% - 61.9% versus placebo, 23.6% - 36.2% versus ezetimibe and 20.4% - 49.2% versus statin up titration.

Safety of alirocumab

Adverse events were generally balanced across treatment arms in the safety population. Common adverse events attributed to alirocumab as reported in the summary of product characteristics (SPC) are upper respiratory tract symptoms and signs, pruritus and injection site reactions. Serious adverse events were reported in 13.3% of patients receiving any control and 13.6% of patients receiving alirocumab. None of the potential risk considered to be associated with low LDL-C levels were confirmed. However the effect of long term exposure to alirocumab or to ultra-low LDL-C levels is unknown.

2. Cost effectiveness of alirocumab

Methods

The applicant presented cost-effectiveness estimates for the HeFH and secondary prevention populations but not for the non-FH primary prevention population. During the review process, the applicant suggested a further refinement of the reimbursement

populations based on the severity of cardiovascular disease and baseline LDL-C as shown in Table 1.

Table 1 Applicant's proposed reimbursement Populations

Population	LDL-C Threshold
Primary Prevention FH (HeFH-PP)	*≥5mmol/L*
Secondary Prevention FH (HeFH-SP)	≥3.5mmol/L
High Risk CVD[1]	*≥4mmol/L*
Recurrent Event /Polyvascular	*≥3.5mmol/L*

[1] High risk of cardiovascular disease is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina requiring hospitalisation), coronary or other arterial revascularisation procedures, chronic heart disease, ischaemic stroke, peripheral arterial disease.

A Markov cost utility model comparing alirocumab to placebo from the perspective of the HSE was submitted. While ezetimibe is also a relevant comparator, the RG are satisfied with ezetimibe's exclusion provided that reimbursement criteria reflect LDL-C treatment thresholds post statin and ezetimibe therapy. Events modelled included revascularisation, ACS, ischaemic stroke, cardiovascular and non-cardiovascular death. The cycle length was one year with a lifetime time horizon. Costs and QALYS were both discounted at 5%.

Population Characteristics

The RG had concerns about the baseline LDL-C applied for each of the cohorts. The applicant applied the average baseline LDL-C of the patients who were above the relevant threshold in the THIN database. The RG considered the modelled baseline LDL-C should be the proposed reimbursement threshold and this is modelled in the preferred base case.

The RG also had concerns in relation to the starting age of the cohort modelled, the ambiguous subgroup definitions used to define cohorts, subgroup heterogeneity and non-mutually exclusive subgroups (the baseline risk associated with polyvascular patients is incorporated into the derivation of baseline risk for the high risk subgroup).

Baseline Risk

Baseline transition probabilities for multiple cohorts were derived from THIN – a UK general practice database using Kaplan Meier analysis. Baseline risk estimates from Mohrschladt et al were used for the derivation of HeFH Risk. It is important to note that Mohrschladt risk estimates are only used to inform transitions from an initial health state. Transitions from every other acute and stable state are estimated from non-FH populations adjusted upwards in an attempt to account for the higher LDL-C in the HeFH populations. The RG felt that the HeFH-secondary prevention model lacked face validity because of the inconsistencies in the resulting event rates.

In addition the RG had concerns in relation to some of the adjustments made to the baseline risk estimates, especially in relation to LDL-C. The baseline risk for each cohort was attributed to the average LDL-C of the cohort. When analysing the cost-effectiveness at a different baseline LDL-C values, the applicant used the Cholesterol Treatment Trialists Collaboration (CTTC) rate ratios per 1mmol/L change in LDL-C to adjust the baseline rate up or down. Whilst the RG acknowledged that patients with higher LDL-C concentrations will

have a higher cardiovascular risk it queried the application of CTTC rate ratios to adjust cardiovascular risk. The RG also had concerns regarding the age and recurrent events adjustments applied in the model.

Treatment Effectiveness

Since a CV outcomes trial for alirocumab has yet to be completed, the manufacturer modelled a reduction in CV events through the surrogate endpoint of LDL-C where LDL-C lowering efficacy estimates were derived from meta-analyses of trials conducted in the ODYSSEY program taking into account the populations, comparators and background treatment in each of the trials. To translate the reduction in LDL-C to a reduction in CV events, estimates from a Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis linking absolute LDL-C changes to changes in first CV event rates were utilised. Different rate ratios were applied depending on the type of cardiovascular event.

The RG noted that the model applies an average trial percentage LDL-C reduction in all patients. Therefore patients with a high baseline LDL-C have a greater absolute reduction in LDL-C compared to patients with lower LDL-C. As the effectiveness of the intervention is translated through absolute LDL-C reduction, a greater absolute treatment effect is applied as a patient's baseline LDL-C increases. However in the FOURIER outcomes trial of evolocumab (PCSK9 inhibitor) there was no increase in treatment effect observed as baseline LDL-C increases. In addition the point estimate of the treatment effect decreases across baseline LDL-C quartiles. The cause of assumption failure is unknown from the published data but a difference in the percentage LDL-C lowering across quartiles may account for some of the differences.

Other model aspects

Health benefits were measured in quality adjusted life years (QALYs) and were accrued by the cohort according to the time spent in each health state and age at time of events. The model applied drug acquisition, hospitalisation costs and post-event costs.

Results

Under the applicant's set of assumptions, the ICER for a mixed secondary and HeFH population is €215,108/QALY. (Incremental Cost €85,678, incremental QALYs 0.40). The RG consider this mixed population to be too heterogeneous for decision making.

The NCPE made a number of amendments to the model including the removal of the CV mortality treatment effect, amending the baseline LDL-C to the LDL-C treatment threshold, adjusting the LDL-C lowering efficacy for baseline LDL-C, changing the HeFH – PP starting age to 30 years and removing the recurrent events risk increase for the polyvascular population.

Despite these changes, the RG do not consider the ICER's generated using either set of assumptions to be robust. The incremental analysis of costs and QALYs of the four populations considered by the applicant under the list price may be found in Table 2.

Table 2 Alirocumab vs Placebo ICERs under the list price

Population	LDL-C Threshold	NCPE Preferred Assumptions			Applicant Submissions		
		Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
Primary Prevention FH	*≥5mmol/L*	€122,364	0.21	€581,009	€102,772	1.17	€87,697
Secondary Prevention FH	≥3.5mmol/L	€93,390	0.22	€426,323	€95,408	1.21	€79,040
High Risk CVD	*≥4mmol/L*	€77,507	0.13	€596,001	€82,399	0.82	€100,678
Recurrent Event /Polyvascular	*≥3.5mmol/L*	€70,155	0.12	€607,351	€74,891	0.81	€92,476

Sensitivity analysis

The uncertainty associated with the ICERS was explored using one-way sensitivity analysis and scenario analysis. The main drivers of cost effectiveness were the baseline risk, the treatment effect ratios, the baseline LDL-C and the LDL-C reduction. There are substantial differences between the ICERs under the NCPE and manufacturer preferred assumptions. The largest driver of the discrepancy is the CV mortality treatment effect applied. Using the CTTC CV mortality rate ratio in the NCPE preferred assumptions for the polyvascular population reduces the ICER to €131,771.

The second major driver of the divergence is the baseline LDL-C assumption. Applying an average baseline LDL-C (4.3mmol/L) for a treatment threshold of 3.5mmol/L instead of the treatment threshold itself reduces the ICER to €433,437 – a reduction of 28%. Probabilistic ICERs are similar to deterministic ICERs. Under the RG's preferred set of assumptions the probability of cost-effectiveness is zero at thresholds of €20,000 or €45,000 per QALY.

3. Budget impact of alirocumab

The proposed ex-manufacturer price of alirocumab is €450.28 per 2 x 1ml auto injector pen at both the 75mg and 150mg strengths. This equates to a 4 week supply on a fortnightly dosing schedule. The total cost per patient per year on the HTDS including 8% wholesale mark-up, 5.25% rebate and patient care fee is €6,799 (€8,238 when VAT included).

The manufacturer estimates a 5 year gross drug budget impact of €38.4million which differs significantly from the NCPE gross drug budget impact ranging from €152.3 million to €258 million over 5 years.

4. Patient Submissions

No patient submissions were received.

5. Conclusion

Following NCPE assessment of the company submission, alirocumab (Praluent®) is not considered cost effective for the treatment of primary hypercholesterolemia and mixed dyslipidemia and is therefore not recommended for reimbursement. The NCPE recommends a further assessment of alirocumab following publication of the ODYSSEY OUTCOMES trial which examines alirocumab's effect on cardiovascular morbidity and mortality.