Aberdeen HTA Group

Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

Erratum

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This document is intended to replace pages 8, 21, 41, 45, 62, 79, 87, 122, 143, 146, 151 and 177 of the original ERG assessment report for *Alirocumab for treating primary hypercholesterolaemia and mixed hypercholesterolaemia*, which contained a few inaccuracies. The main issue relates to a model input error in the ERG's calculations behind two of the ICERs reported in Table 55 of the ERGs original report (page 151). These are additional scenario analyses (with rate ratios per 1.0 mmol/L, reduction taken from the CTT meta-analysis) for alirocumab versus ezetimibe in statin intolerant patients with HeFH (primary prevention) and HeFH (secondary prevention). This also had implications for text on page 146 of the report. In addition, we amended a number of further minor (typographical) errors identified in the report. The amended pages follow in order of page number below.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG considers the submitted model to be of good quality and the structure is generally appropriate. Significant effort has gone into informing the model with real world risk data for relevant UK populations. Based on comparing survival from the model with published survival data for UK cohorts, there is good agreement with medium term survival expectations for the high risk CVD and recurrent CV events cohort, and particularly ACS cohorts. The utility weights incorporated in the model were coherent, from a single UK population based source. Appropriate age adjustment was conducted. The ERG has a number of concerns with some of the parameter estimates and base case assumptions applied in the model as detailed below:

- The model structure uses a composite event states for ACS which includes MI and unstable angina (UA). This makes it impossible to model different effects for MI and UA (see below)
- Two options were presented by the company for the secondary prevention HeFH analysis; one using CV risks estimated from analysis of THIN data, and the other using CV risk estimated from a previous published study. The composite annual baseline CV risk using the latter approach is more than twice as high. The ERG has been unable to verify which is more appropriate.
- Costs for the stroke and post-stroke health states appeared low and inconsistent with estimates based on UK population data and values applied in previous technology appraisals.
- Also related to the application of post-CV event costs, it appeared inconsistent with previous technology appraisals, that these should only be applied to 2 years following a CV event (as they were in the company's analysis), particularly for stroke which may result in long-term social care costs.
- The LDL-C threshold applied for the high risk CV cohort in the base case analysis appeared very restrictive, particularly given that statin + ezetimibe is a valid comparator in this population. The base case results for this cohort apply only to those with LDL-C $\geq$ 3.36 mmol/L on maximally tolerated statin. The ERG suspects that a very low proportion of patients in the wider high risk CVD population would meet these criteria. This raises a question over the relevance of the base case analysis for the high risk CVD population. Moreover, if alirocumab is being positioned as an adjunct to statin alone in

According to the Summary of Product Characteristics the usual starting dose for alirocumab (Praluent) is 75 mg administered subcutaneously once every 2 weeks. Patients requiring larger LDL-C reduction (>60%) may be started on 150 mg administered subcutaneously once every 2 weeks. The dose can be individualised based on patient characteristics such as baseline LDL-C level, goal of therapy, and response.

Lipid levels can be assessed four weeks after treatment initiation or titration, when steady-state LDL-C is usually achieved, and dose adjusted accordingly (up-titration or down-titration). Patients should be treated with the lowest dose necessary to achieve the desired LDL-C reduction.

In all patients, it is anticipated that alirocumab will be used continuously once initiated.

Most common adverse reactions with alirocumab include local injection site reactions, upper respiratory tract signs and symptoms, and pruritus.Generic allergic reactions include pruritus, as well as rare and sometimes serious allergic reactions such as hypersensitivity, nummular eczema, urticaria, and hypersensitivity vasculitis. If signs or symptoms of serious allergic reactions occur, treatment with alirocumab must be discontinued and appropriate symptomatic treatment initiated. Full details of adverse reactions and contraindications are given in the Summary of Product Characteristics.

The list price acquisition cost is £168 per one-pen pack and £336 per two two-pen pack (Table 5 of the company's submission). The company has recently agreed a patient access scheme with the Department of Health.

3.3 Comparators

The NICE final scope specified optimised statin therapy as a comparator, without any further qualifying criteria in terms of previous or current treatment or its effectiveness. The company did not consider this specific configuration of comparator. However, optimised statin therapy was one of two comparators specified by the company for people whose LDL-C was not adequately controlled with optimised (maximum tolerated dose) statin therapy. Both the NICE final scope and the company's

Study ID (trial acronym)	**Intervention**	**Number of patients**	**Study population** (LDL-C in mmol/L)	**Primary outcomes**	**Treatment duration**	**Funders**
	Placebo	107	*Mean LDL-C*: 2.646 (SD 0.820) *HeFH*: not reported *Mean age:* 63 (SD 9.3) *White race*: 258 (81.6%) *CHD:* 247 (78.2%) *CHD risk equivalents:* 136 (43.0%)			
Robinson 2015[69] (LONG TERM)	Alirocumab 150 mg (Q2W)	1553	LDL-C≥1.8 (70 mg/dL) with or without established CHD or CHD risk equivalents *Mean LDL-C*: 3.171(SD 1.092) *HeFH*: 415 (17.7%) *Mean age:* 60.5 (SD 10.4) (range 18-89) *White race*: 2171 (92.7%) *CHD:* 1607 (68.6%) *CHD risk equivalent:* 962 (41.1%)	% change in calculated LDL-C from baseline to week 24	78 weeks	Sanofi and Regeneron
	Placebo	788				
Alirocumab vs active agent						
Bays 2014 [39] (OPTIONS I)	Alirocumab 75-150 mg Q2W plus atorvastatin 20 mg QD	57	Prior CVD with LDL-C=1.8 (70 mg/dL) or CVD risk factors with LDL-C=2.6 (100 mg/dL); stable atorvastatin 20 or 40 mg/day *Mean LDL-C*: 2.723 (SD 0.884)	% change in calculated LDL-C from baseline to week 24	24 weeks	Sanofi and Regeneron
	Alirocumab 75-150 mg Q2W plus atorvastatin 40 mg QD	47				
	Ezetimibe 10 mg QD plus	55				

4.1.5 Critique of data extraction

The ERG considers the methods described in company's submission to be appropriate. Two reviewers independently selected studies and extracted data with any discrepancies resolved by discussion between the two reviewers. Any unresolved issues were adjudicated by a third reviewer.

4.1.6 Quality assessment

The quality of the relevant studies was assessed according to the Cochrane Collaboration's tool for assessing risk of bias of RCTs. The criteria involved assessment of selection bias, performance bias, detection bias, attrition bias, reporting bias and other potential biases. The number of reviewers involved in the quality assessment of the selected studies was not detailed in the submission.

The ERG conducted a broad assessment of the methods used by the company for the systematic review of clinical effectiveness evidence using the CRD criteria. Results are shown in Table 4.

Table 4 Quality assessment of the company's systematic review

CRD quality item	Score
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	No*
5. Are the primary studies summarised appropriately?	No*

*Only details of the 10 trials from the ODYSSEY programme are provided but not those of all studies identified by the literature searches

Inclusion/exclusion criteria relating to the primary studies which address the review question are clearly described in Appendix 6 of the company's submission. As highlighted in section 4.1.2, two systematic reviews - with two different sets of inclusion criteria - were conducted by the company: **Review 1** focused on patients at *high risk of CVD* and Review 2 focused on patients *at moderate to high risk of CVD*.

- Baseline Lp(a): various depending on trial (see Table 32, CS)
- Baseline total PCSK9 level: <median, ≥median
- Baseline free PCSK9 level: <median, ≥median

In general, the effect of alirocumab versus its comparators was consistent between subgroups. No further details are provided by the ERG.

Pooled-analysis

The company indicated they undertook some pre-specified pooled analysis for the following trials' populations:

- FH I and FH II for HeFH patients
- ALTERNATIVE and MONO for efficacy versus ezetimibe in patients not receiving statins
- OPTIONS I and OPTIONS II for alirocumab as add on to statin, ezetimibe as add on to statin and statin up titration.

The company indicated that each pooled analysis used individual patient data and results were presented for the primary endpoint and for key secondary efficacy endpoints.

In addition, the company undertook pooled analysis to look at two dosing regimens:

- Alirocumab 75 mg 2QW as initiation dose with potential up titration to 150 mg Q2W (FH I, FH I, COMBO I in combination with statins vs placebo; ALTERNATIVE, MONO without statins vs ezetimibe; COMBO II, OPTIONS I, OPTIONS II in combination with statins vs ezetimibe)
- Alirocumab 150 mg 2QW as initiation dose (LONG TERM, HIGH FH in combination with statins vs placebo).

The results of these various pooled analyses are shown in Table 17 for comparisons at 24 weeks.

appropriately applied to reflect the fact that, in reality, patients move continuously between states over time.

The ERG consider the company's model structure to be generally appropriate to the decision problem, and acknowledge the value of separating the post-event health states into three sub-states reflecting time since the event. One potential problem related to the use of a composite event state for ACS which includes MI and unstable angina (UA). This makes it impossible to model different treatment effects for MI and UA, which is problematic because the primary source of effectiveness data suggests different degrees of uncertainty for these effects. There are also a few limiting structural assumptions which may be conservative. One relates to the omission of TIA and stable angina (although the latter may be partially captured by elective revascularization), and the other relates to the fact that the model has limited capacity to capture multiple CV event histories in terms of their cumulative impact on costs and quality of life (due to the memoryless property of Markov models). For example, patients in the post-stroke state who experience an ACS event, then go on to attract the event costs that reflect average values following the ACS event, and not the expected costs for patients with a history of stroke and ACS. It is possible that these assumptions may somewhat underestimate QALY gains and downstream cost savings associated with more effective treatments. One issue which has the potential to bias in favour of alirocumab is the omission of any treatment emergent adverse event (TEAE) states. The available safety data suggests no significant difference in the percentage of patients experiencing any TEAE, although it does indicate an incidence of injection site reactions of 6 per 100 patient years in the pooled alirocumab data (Table 48 of the company's submission). Whilst the severity of these was reported as generally mild and transient, it is unclear what the cost implications were. It is perhaps reasonable to assume that these would require at most a GP visit and so would be unlikely to have significant impact on cost-effectiveness. General allergic events were also more commonly reported for alirocumab (primarily pruritis), but pooled incidence was low (0.8-1.1%) and severity typically mild.

The two HeFH populations (primary and secondary prevention) are modelled individually, while the high risk CVD population consists of a mixed cohort based on the distribution CV event histories observed in the THIN database. Table 23 presents the relevant proportional distribution. The effect of alirocumab treatment is assumed to be independent of patients' baseline characteristics in the model, i.e. homogenous treatment effects are applied.

Table 23 High risk CVD cohort proportions by patient types (Source: Table 59 of the company's submission)

ACS ≤12 months prior to index	3.28%
ACS 12–24 months prior to index	2.83%
Ischaemic Stroke	11.05%
Other CHD	68.55%
PAD	14.29%

ACS, acute coronary syndrome; CHD, coronary heart disease; CVD, cardiovascular disease; IS, ischaemic stroke; PAD, peripheral arterial disease

5.2.4 Interventions and comparators

The intervention - alirocumab alone or in combination with a statin, with or without ezetimibe, or in combination with ezetimibe – is in line with the final scope. Alirocumab in the company's submission is considered in line with its marketing license - "*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 statin (when used as recommended by treatment guidelines); or alone or in combination with other lipid-lowering therapies in patients who are statin intolerant or for whom a statin is contraindicated*" - for patients with primary hypercholesterolaemia who are failing to reach LDL-C goals. The company's submission states that it was assumed that in clinical practice alirocumab will only be prescribed in high risk, high unmet need patients, and will be supported by a homecare delivery service and patient support programme. In the main analyses, alirocumab is modelled as adjunctive treatment for those whose LDL-C is not adequately controlled on statin (+/-) ezetimibe, or ezetimibe alone in those who are intolerant to statins. However, in line with the scope, the company also presents an additional set of comparisons where alirocumab is compared directly against ezetimibe; i.e. as an alternative to ezetimibe

clinical outcomes were presented for each strategy. Total QALYs accrued in the different health states were also summarised for the alirocumab and comparator arms.

The company's estimated base case results are replicated for each patient population in Table 38.

The base case analyses for HeFH are provided for cohorts aged 50 (primary prevention) and 60 (secondary prevention), LDL-C ≥ 2.59 mmol/L (mean LDL-C = 4.82 mmol/L for primary prevention, 4.56 for secondary prevention), 50% male. For alirocumab used as an add-on to current maximal LMT (maximal dose of statins combined with ezetimibe) the ICER is £36,793 in the primary prevention HeFH population. For the secondary prevention HeFH cohort, the estimated ICER is £16,896 based on CV risks data from Morschladt et al.97.

The base case analysis for high risk CVD is conducted for a cohort aged 65 years, 60% male, LDL-C ≥ 3.36 mmol/L. The recurrent events/ polyvascular disease cohort has the same characteristics, except an LDL-C threshold of 2.59 mmol/L is applied (mean = 3.31 mmol/L).

For the high risk CVD cohort, the estimated ICER for alirocumab as an add-on to maximal statin treatment is £19,751. For the cohort with recurrent events/ polyvascular disease, the corresponding ICER is £19,447.

5.2.11 Model validation and face validity check

The company's submission describes how three advisory boards were held as part of the model development process. Additional consultation was sought from clinical experts and health economists to inform key parameters. The company assessed the internal validity of the model using extreme value checks, Markov traces and tracing of the estimated QALYs and costs over time. Structural sensitivity analyses were performed, as were deterministic and probabilistic sensitivity analysis, to assess the impact of changes on results.

In terms of the model face validity, the ERG believes that the structure of the model and the possible transitions are plausible. The ERG has performed internal consistency checks on the model and have identified no internal programming errors. The ERG can replicate all the company's results. An appropriate UK primary care database was used by the company to inform the model parameters in terms of baseline CV event rates. However the estimated CV events rates were not estimated from subpopulations with characteristics (i.e. baseline LDL-C and age) exactly matching those of the modelled cohorts, but were rather calibrated to the selected model age and LDL-C levels using published statistical relationships. In light of data limitations, this does seem reasonable. The baseline LDL-C adjustments in have been applied using a well-accepted relationship[31 32 99 100] between statin induced reduction in LDL-C and CV event rates. The ERG had some concerns relating to the inflation of subsequent events following recurrent ACS and ischaemic stroke, but have performed sensitivity analysis the results are not heavily influenced by this parameter. It also seems reasonably well justified to inflate these risks in the model.

The company did not assess the external or cross validity of their model. Since the company had access to THIN data, it might have been possible to generate longer-term survival curves of time to CV events, and then cross checked these against those predicted by their model over equivalent time horizons. The ERG has cross checked the composite baseline probabilities of CV events for the modelled high risk CVD population, and these do appear to be generally consistent with those used to represent baseline (of treatment) risks in previous models.[29] Given that the modelled patient populations represent those who have high baseline LDL-C despite current LMT, it doesn't seem unreasonable that they should have similar risks to the mean off-

prevention (Table 50). Finally, given the uncertainty surrounding the relationship between LDL-C reductions achieved with alirocumab and proportional CV event rates, we present a further more conservative scenario analysis with the updated model for each comparison; here we model all the effects for alirocumab through the estimated relationships from the CTT meta-analysis (as per one of the company's scenario analysis).

5.3.1 The ERG updated base case and scenario analysis (deterministic)

The following Tables present the company's base case ICERs (Table 50) and then the ERGs updated base case; incorporating points 1-7 above with the company's preferred approach of scaling the hazard ratios from Navarese et al.[82] (Table 51). The results in Table 52 then present the more conservative scenario using the CTT meta-analysis to model all effects of alirocumab on CV events. Tables 53 to 55 then present the corresponding ICERs for statin intolerant patients.

With the ERGs updated base case, the ICERs are remain very similar to the company's base case ICERs (Tables 51). As an add-on to optimal statin therapy (+/- ezetimibe), they are below £20,000 in the HeFH secondary prevention, high risk CVD, and recurrent CVD/polyvascular disease populations. The ICER remains above £30,000 in the HeFH primary prevention population (Table51). The ICERs also remain below £20,000 for the statin intolerant CVD cohorts (Table 54).

Consistent with the company's scenario analysis, using the CTT to model the effects of alirocumab on CV event rates raises the ICERs above £30,000 for alirocumab as an adjunctive to maximally tolerated statin therapy (Table 52) - although the ICER in the HeFH secondary prevention cohort is close to £30,000 (£33,339) using the risk data from Morschladt et al. Using the CTT approach for statin intolerant patients, the ICERs are slightly above £30,000 in the high CV risk, and the recurrent CVD/polyvascular disease populations (Table 55). Note the ICERs for the statin intolerant HeFH populations are based on the ERGs assumption of a baseline LDL-C of 5.8 (assumed 20% reduction from the baseline value of 7.27 reported by Morschladt et al.)

Table 55 The ERG additional scenario analysis results (with rate ratio per 1.0 mmol/L reduction from CTT meta-analysis) – *statin intolerant patients*

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (LDL-C ≥2.59 mmol/L) *	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	22,228	0.51	0.49	45,786
	Ezetimibe	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) Baseline risk data from Morschladt et al. *	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	17,332	0.91	0.79	22,042
	Ezetimibe	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) Baseline risk data from THIN*	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	18,329	0.87	0.71	25,869
	Ezetimibe	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥3.36 mmol/L) **	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	17,721	0.64	0.51	34,600
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L) ***	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	16,400	0.66	0.49	33,519
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year
*Mean baseline LDL-C=5.8 mmol/L; **Mean baseline LDL-C=4.55 mmol/L; *** Mean baseline LDL-C=4 mmol/

There was no evidence of differences between groups in the rates of adverse events or mortality.

The ERG considered that the company's systematic reviews of clinical evidence were broadly adequate.

With regard to the economic model, the ERG considers it to be of good quality and in general appropriately structured. The one main structural concern relates to the use of a composite event state for ACS which includes MI and unstable angina (UA). This makes it impossible to model different effects for MI and UA. Significant effort has gone into informing the model with real world risk data for relevant UK populations – although this has to be recalibrated to the age and LDL-C levels of the modelled populations. Based on comparing survival from the model with published survival data for UK cohorts, there is good agreement with medium term survival expectations for the high risk CVD and recurrent CV events cohort, and particularly ACS cohorts. The utility weights incorporated in the model were coherent, from a single UK population based source. Whilst the ERG had a number of concerns with some of the parameter estimates and base case assumptions, one of these in particular appeared to have critical impact on the estimated base case ICERs: the method used to extrapolate LDL-C reductions mediated through PCSK9 inhibitors to relative reductions in CV event rates.

6.1 Implications for research

There is extensive research already ongoing related to PCSK9 inhibitors, and outcome data are awaited from this. In particular, the results of the CVOT ongoing trial, which are due to be reported in January 2018, will provide useful information on the effect of alirocumab on CV events. Nevertheless, given the novelty of PCSK9 inhibitors and consequent treatments aimed at them, 'off target' effects will be particularly important to collate. There is also a need to further assess the cost-effectiveness of alirocumab, both as monotherapy and in combination, in a variety of potential relevant patient groups, when the results of CV outcome trials become available (e.g. familial dyslipidaemias, existing cardiovascular disease).