



Cost-effectiveness of evolocumab (Repatha®) for primary hypercholesterolemia and mixed dyslipidemia.

The NCPE has issued a recommendation regarding the cost-effectiveness of evolocumab (Repatha®). Following NCPE assessment of the applicant's submission, evolocumab (Repatha®) is not considered cost-effective for the treatment of primary hypercholesterolemia and mixed dyslipidemia 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 (Amgen) economic dossier on the cost effectiveness of evolocumab (Repatha®). 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.

Summary

In November 2015, Amgen submitted a dossier to examine the cost effectiveness of evolocumab under the High Tech Drug Scheme. Evolocumab is licensed in combination with a statin and other lipid lowering therapies for patients unable to reach LDL-C goals with the maximum tolerated statin dose. The effect of evolocumab on cardiovascular morbidity and mortality has yet to be determined. It is administered as a subcutaneous injection at a dose of 140mg every two weeks (Q2W) or 420mg once monthly (QM). The applicant presented the cost-effectiveness of evolocumab for subgroups of the licensed population; those with an LDL-C >3.5mmol/L (after statin and other lipid modifying therapy) with a previous history of cardiovascular disease and those with heterozygous familial hypercholesterolemia (HeFH).

1. Comparative effectiveness of evolocumab

The clinical development program evaluated evolocumab in a two weekly (Q2W) or monthly (QM) dosing regimen in over 10 trials. The four primary trials were international, multicentre phase 3 randomised control trials (RCTs) of 12 weeks (LAPLACE-2, RUTHERFORD-2 and GAUSS-2) and 52 weeks (DESCARTES) duration.

The LAPLACE-2 trial evaluated the effect of evolocumab in patients with and without cardiovascular disease (CVD). Patients were randomly assigned to receive one of five statin dose combinations. Patient's LDL-C levels were allowed to stabilise again before successful patients were randomised to receive evolocumab (Q2W or QM) or comparator (placebo or ezetimibe) in an approximate 2:1 ratio. Only 125 (6.6%) of the total participants were secondary prevention patients with an LDL-C >3.5mmol/L.

RUTHERFORD-2 evaluated evolocumab versus placebo in patients with HeFH (as defined by Simon Broome Criteria). Patients with and without CVD were included and were required to have a fasting LDL-C \geq 2.6mmol/L with stable background lipid lowering therapy. 329 patients were randomised in a 2:1 ratio to evolocumab (Q2W or QM) or placebo (Q2W or QM).

GAUSS-2 was designed to evaluate the efficacy of evolocumab versus ezetimibe in patients with statin intolerance. Statin intolerant patients were defined as those who had tried two or more statins and were unable to tolerate any statin dose or an increase in dose above a stated total weekly maximum dose for each statin. Therefore background therapy for some patients consisted of low dose statins (17-20% of patients). 309 patients were randomised in a 2:1 ratio to evolocumab (Q2W or QM) or ezetimibe (Q2W or QM).

DESCARTES was designed to evaluate the safety of evolocumab over one year. Patients were stratified according to the level of CV risk and allocated to the following groups accordingly: diet alone, diet plus atorvastatin 10mg, diet plus atorvastatin 80 mg or diet plus atorvastatin 80 mg daily plus ezetimibe 10 mg daily each for a run-in period of 4 to 12 weeks. 905 patients with an LDL cholesterol level >1.9 mmol/L or higher were then randomly assigned in a 2:1 ratio to receive either evolocumab (420 mg QM) or placebo every 4 weeks.

Results

The co-primary endpoints were percent change from baseline in LDL-C at week 12 (DESCARTES) and mean of weeks 10 and 12 (LAPLACE-2, GAUSS-2, and RUTHERFORD-2). As well as reducing LDL-C, evolocumab was also superior to placebo and ezetimibe in improving other lipid parameters including non-HDL-C, ApoB, Lp(a) and triglycerides. LDL-C efficacy results are shown in Table 1 and 2.

Table 1 Mean percent change in reflexive LDL-C from baseline at the mean of weeks 10/12 (FAS).

	RUTHERFORD-2		GAUSS-2		LAPLACE-2	
	Placebo Q2W	Evolocumab 140 mg Q2W	Ezetimibe	Evolocumab 140mg Q2W	Ezetimibe	Evolocumab 140mg Q2W
Mean of weeks 10/12 mean percent change from baseline (95% CI)	-1.08 (-5.84, 3.67)	-61.23 (-64.61, -57.85)	-17.94 (-21.03, -14.86)	-56.11 (-59.73, -52.49)	-20.36 (-23.84, -16.88)	-61.32 (-63.05, -59.58)
CI, confidence interval; FAS, full analysis set; Q2W, every other week;						

Table 2 Mean percent change in ultracentrifugation LDL-C from baseline at week 12 and 52 DESCARTES (FAS).

	Placebo QM (N=302)	Evolocumab QM (N=599)
Week 12 mean percent change from baseline (95% CI)	3.2 (0.6, 5.7)	-54.4 (-56.2, -52.5)
Week 52 mean percent change from baseline (95% CI)	6.8 (3.4, 10.3)	-50.1 (-52.6, -47.7)
CI, confidence interval; FAS, full analysis set; N, number of subjects randomised and dosed in the full analysis set; QM, monthly		

The applicant's submission also provided evidence for the efficacy and safety of evolocumab in patients with homozygous FH (HoFH)

- TESLA, a double blind placebo-controlled RCT specifically in 49 patients with HoFH showed that compared to placebo, evolocumab reduced LDL-C by 31% at week 12.
- TAUSIG, a non-randomised, non-controlled study which showed reductions of approximately 23% to 30% in 66 patients with HoFH not on apheresis.

The review group (RG) had a number of concerns with the clinical evidence presented:

- There is uncertainty in relation to the magnitude of LDL-C reduction across different LDL-C subgroups. A reduction in LDL-C was consistently demonstrated across LDL-C subgroups for evolocumab vs ezetimibe and vs placebo. However, there is limited power to detect subgroup effects due to small sample sizes. In a trial of another PCSK9 inhibitor (alirocumab), the magnitude of LDL-C reduction was lower in higher baseline LDL-C quartiles.
- The main limitation of the clinical trials completed to date is the reliance on the surrogate endpoint LDL-C instead of cardiovascular outcomes. While there is a significant body of evidence supporting this endpoint, FDA committee members (including those who supported approval) emphatically stated that LDL-C levels were not a reliable surrogate for cardiovascular benefit.

2. Safety of evolocumab

Adverse events were generally balanced between evolocumab and comparator arms. Common adverse reactions for evolocumab as listed in the summary of product characteristics (SPC) include influenza, nasopharyngitis, upper respiratory tract infection, rash, nausea, back pain, arthralgia and injection site reactions. Most adverse events were mild to moderate in severity. Serious adverse events were reported in 2.8% of patients in the any evolocumab group and 2.1% of patients receiving any control. There was a higher incidence of adverse events in the DESCARTES trial which is likely due to its longer follow up of 52 weeks compared to 12 weeks in the other trials.

3. Cost effectiveness of evolocumab

Methods

The analysis examined the cost effectiveness relative to two comparators; ezetimibe where evolocumab use displaces ezetimibe therapy and placebo in situations where evolocumab use is assumed to be used in addition to ezetimibe and statins (where tolerated). The baseline LDL-C value applied in the model reflects its value after treatment with background lipid lowering therapy. The baseline LDL-C evolocumab treatment threshold proposed by the applicant and applied in the model base case is 3.5mmol/L. The analysis was repeated for four populations:

- Secondary prevention statin tolerant non-FH
- Secondary prevention statin intolerant non-FH
- Secondary prevention HeFH
- Primary prevention population HeFH.

A Markov state transition model was presented in Microsoft Excel with a one year cycle length and a lifetime time horizon. The primary health states in the model included no CVD, established CVD (ECVD), Acute Coronary Syndrome (ACS), Post-ACS, Ischaemic Stroke (IS), Post IS, Heart Failure (HF), Post-HF and death. In addition to these health states the model contained 13 combined health states which could include any logical combination of acute and post-CVD health states resulting in a total of 24 health states.

The process of estimating the baseline event rate was complex. The probability of a cardiovascular event was estimated by applying risk equations to the comparable evolocumab trial population. The risk was then adjusted for age and multiplied by a calibration factor derived by the applicant. The RG felt that the general modelling approach of estimating the baseline risk using risk equations was appropriate but had concerns in relation to the selection and subsequent treatment of them. The model structure does not adjust cardiovascular risk in patients with higher LDL-C which is a limitation of the model. The starting age of treatment was also identified by the RG as an important factor in the modelling exercise.

To translate the reductions in LDL-C to reduction in CV events, estimates from a Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis published in 2010 linking absolute LDL-C changes from statins to changes in first CV event rates were utilised by the applicant. The rate ratio reduction varied according to CV event type. 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 their age at that time of events. The model applied drug acquisition, monitoring costs, hospitalisation costs and post-event costs. The RG had concerns about the application of revascularisation costs in the model.

The RG re-ran the model using the NCPEs preferred set of assumptions.

Results

The ICER's below reflect the incremental cost per QALY versus ezetimibe and versus placebo at an LDL-C of 3.5mmol/L under the NCPE's and the applicants preferred assumptions.

Table 3 Base Case ICER vs Ezetimibe under the HTDS list price with a Baseline LDL-C of 3.5mmol/L

	NCPE Preferred Assumptions			Applicant Submission		
	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
<i>Non-Familial Secondary Prevention Statin Tolerant (LAPLACE-2 SP)</i>	€70,047	0.17	€406,067	€68,044	0.23	€290,037
<i>Non-Familial Secondary Prevention Statin intolerant (GAUSS-2 SP)</i>	€65,282	0.23	€286,182	€62,693	0.26	€238,308
<i>HeFH Secondary Prevention (RUTHERFORD-2 SP)</i>	€73,366	0.25	€294,783	€69,166	0.30	€232,178
<i>HeFH Primary Prevention (RUTHERFORD-2 –PP)</i>	€96,243	0.21	€452,741	€80,498	0.52	€153,386

Table 4 Base Case ICER vs Placebo under the HTDS list price with a Baseline LDL-C of 3.5mmol/L

	NCPE Preferred Assumptions			Applicant Submission		
	Δ Cost	Δ QALY	ICER	Δ Cost	Δ QALY	ICER
<i>Non-Familial Secondary Prevention Statin Tolerant (LAPLACE-2 SP)</i>	€75,135	0.27	€276,173	€71,033	0.37	€194,519
<i>Non-Familial Secondary Prevention Statin intolerant (GAUSS-2 SP)</i>	€72,767	0.35	€207,815	€65,575	0.40	€162,626
<i>HeFH Secondary Prevention (RUTHERFORD-2 SP)</i>	€78,314	0.38	€204,700	€70,662	0.46	€153,697
<i>HeFH Primary Prevention (RUTHERFORD-2 –PP)</i>	€103,458	0.35	€299,336	€83,462	0.81	€103,200

Sensitivity analysis

The uncertainties associated with the ICERS were explored using one way-sensitivity analysis and scenario analysis. The ICERs below were calculated using the NCPEs preferred set of assumptions. The ICERs were very sensitive to the co-efficients in the risk equations and the calibration factors applied. The ICER was also sensitive to the background utility value, extent of LDL-C reduction, and the CTTC rate ratios. Increasing the baseline LDL-C treatment threshold reduced the ICER but in the range examined (up to 6mmol/L) the ICER remained substantially above €45,000 even when further restricting the population to those with ACS or Diabetes.

Scenario analysis in the non-familial statin tolerant secondary prevention population showed that the ICER vs ezetimibe was extremely sensitive to:

- The proportion of patients starting in the post-HF health state – where the ICER increased to >€2,000,000/QALY if all patients started in the post-HF health state
- Applying a mortality treatment effect in heart failure health states – this reduced the ICER from €406,067 to €332,639.
- The starting age of the cohort; an average starting age of 30 increased the HeFH-PP ICER vs ezetimibe to over €800,000/QALY.
- The efficacy of evolocumab to reduce LDL-C may be less at higher baseline LDL-C values. If efficacy results from the triple therapy arm of the DESCARTES trial were applied, the ICER versus placebo increases by 20%.

A probabilistic analysis was also conducted. In all scenarios, the probability of cost effectiveness was 0% at a threshold of €45,000/ QALY.

4. Budget impact of evolocumab

The proposed ex-manufacturer price of evolocumab is €440.23 per pack (2 x 140mg syringe or pen). This equates to a 4 week supply based on a fortnightly dosing schedule. The total cost per patient per year on the HTDS including 8% wholesale mark-up, 4% rebate, VAT and high-tech patient care fee is €8,117.87.

Based on a treatment threshold of 3.5mmol/L and restricting reimbursement to the four populations examined in the model, the projected cumulative gross budget impact over the first five years is over €258 million (16.9million in Year 1 rising to 86.8million in Year 5). If the treatment threshold were increased to 4mmol/L the budget impact decreases to €152.3 million. However these figures are associated with much uncertainty.

5. Patient Submissions

No patient submissions were received.

6. Conclusion

Following NCPE assessment of the company submission, evolocumab (Repatha®) is not considered cost-effective for the treatment of primary hypercholesterolemia and mixed dyslipidemia and is therefore not recommended for reimbursement. The NCPE recommend a further assessment of evolocumab following publication of the cardiovascular outcomes trial FOURIER. Results are expected to be announced in March 2017.