Cost-effectiveness of evolocumab (Repatha®) for hypercholesterolemia

The NCPE has issued a recommendation regarding the cost-effectiveness of evolocumab (Repatha®). Following NCPE assessment of the applicant's submission, the NCPE recommends that evolocumab not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

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.

National Centre for Pharmacoeconomics **May 2018**

Summary

In October 2017, Amgen resubmitted a dossier to examine the cost-effectiveness of evolocumab under the High Tech Drug Scheme. In its 2016 assessment the NCPE had recommended a reassessment of evolocumab following publication of the evolocumab cardiovascular outcomes trial FOURIER. This was published in March 2017. Evolocumab is a PCSK9 inhibitor. By inhibiting the binding of PCSK9 to low density lipoprotein cholesterol (LDL-C) receptors, evolocumab increases the number of LDL-C receptors available to clear LDL-C thereby lowering LDL-C levels. 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. Evolocumab is administered subcutaneously 140mg once every two weeks or 420mg once monthly. In this resubmission, the applicant submitted evidence on the cost effectiveness of evolocumab in the following subgroups of the licensed population:

- Atherosclerotic cardiovascular disease (ASCVD Secondary Prevention): Heterozygous Familial Hypercholesterolemia (HeFH) and non-HeFH patients with an LDL-C persistently ≥4mmol/L
- No ASCVD (primary prevention): HeFH patients with LDL-C persistently ≥5mmol/L.

LDL-C levels (in both these subgroups) reflect those on maximum tolerated statin and ezetimibe therapy.

1. Comparative effectiveness of evolocumab

The applicant presented evidence from the FOURIER and GLAGOV randomised controlled trials which were not available at the time of the previous assessment. FOURIER was a randomised placebo controlled double blind multicentre phase 3 study designed to evaluate the efficacy and safety of evolocumab in combination with high to moderate intensity statin therapy in reducing cardiovascular (CV) morbidity and mortality. Eligible patients (who were receiving statin therapy) were randomised in a 1:1 fashion to receive evolocumab (140mg once every two weeks or 420mg once monthly) or matching placebo as subcutaneous injections. A total of 27,564 patients were randomised (13,780 placebo, 13,784 evolocumab). The baseline characteristics across the two groups were well balanced.

Evolocumab significantly reduced the risk of the primary composite endpoint of CV death, myocardial infarction (MI), stroke, hospitalisation for unstable angina or coronary revascularisation (hazard ratio (HR), 0.85; 95% CI, 0.79 to 0.92; p<0.001). Evolocumab also significantly reduced the risk of the key secondary composite endpoint of CV death, MI or stroke (hazard ratio, 0.80; 95% CI, 0.73 to 0.88; (p<0.001)). No treatment interaction effect was observed across baseline LDL-C quartiles for the primary or secondary endpoint. The point estimates move in the opposite direction to what would be expected given the expected relationship between baseline LDL-C, absolute LDL-C reduction and treatment effect. However confidence intervals overlap. The treatment effect of evolocumab on the key secondary composite endpoint was driven by a reduction in MI and stroke. Evolocumab had no observed effect on CV mortality (HR, 1.05; 95% CI, 0.88 to 1.26; p=0.62) or all-cause mortality (HR. 1.04; 95% CI, 0.91-1.19; p=0.54). Health related quality of life was not assessed. Limitations of the clinical evidence included the relatively short duration of the trial (median length of follow up was 2.2years) and therefore the long term effect of evolocumab on cardiovascular morbidity or mortality is unknown. In addition the study was not powered to precisely quantify the magnitude of evolocumab's effect on the ASCVD secondary prevention subgroup with an LDL-C >4mmol/L or evolocumab's effect on the CV mortality individual endpoint.

GLAGOV was a randomised placebo-controlled double-blind phase 3 study designed to evaluate the efficacy of evolocumab in reducing the burden of atherosclerotic disease as assessed by intravascular ultrasonography. Patients undergoing a clinically indicated coronary angiogram with angiographic evidence for coronary atheroma and meeting predefined statin and LDL-C inclusion criteria were eligible for inclusion. A total of 968 patients were randomised in a 1:1 fashion to receive evolocumab 420mg or placebo once monthly for 76 weeks in addition to background optimal statin therapy. The primary end point was the nominal change in percent atheroma volume from baseline to week 78. The treatment difference was -1.01% (95% CI, -1.38%, -0.64%, p <0.001.)

2. Safety of evolocumab

In the assessment of clinical safety in the previous submission there were no serious safety concerns. Common adverse reactions for evolocumab as listed in the summary of product

characteristics are influenza, nasopharyngitis, upper respiratory tract infection, rash, nausea, back pain arthralgia and injection site reactions. Since the previous submission, no substantial safety concerns have been identified. In FOURIER no significant between group differences were seen in overall rates of adverse events or serious adverse events. However injection site reactions were more frequent with evolocumab. A substudy (EBBINGHAUS) was designed to assess cognitive function in a subset of participants. There were no significant between group differences in the primary endpoint of spatial working memory strategy index of executive function score or in secondary endpoints.

3. Cost effectiveness of evolocumab

Methods

A cost-utility analysis comparing evolocumab versus no treatment was conducted under the HSE perspective. Background treatment was modelled to consist of statin and ezetimibe in both arms. The NCPE agreed with the applicant's choice of comparator provided evolocumab ICERs are presented as representing a third line setting when co-prescribed with statin and ezetimibe. Evolocumab is less cost effective in settings where evolocumab displaces ezetimibe. A Markov state transition model was presented with a one year cycle length and a lifetime time horizon. The primary health states in the model included non-CVD, other ASCVD, MI, Post MI, Ischemic Stroke (IS), Post IS, 2+ MIs and 2+ IS and death. In addition to these health states the model contained 10 combined health states which could include any logical combination of acute and post-CVD health states resulting in a total of 22 health states.

The applicant made significant changes to how baseline risk was derived compared to the previous submission. Baseline cardiovascular risk and adjustment for cardiovascular history and age were derived from analysis of UK general practice database. The applicant adjusted the baseline event rate for higher LDL-C by using the composite (0.78) rate ratio from the Cholesterol Treatment Trialists collaboration (CTTC) 2010 meta-analysis. The NCPE had a number of concerns regarding derivation of the baseline risk including the double counting of the effects of age on baseline rate, poor quality reporting of regression methods used, face validity of non-CV mortality rates, baseline LDL-C risk adjustments and double counting in the derivation of HeFH risk estimates.

The applicant did not apply evolocumab treatment effect hazard ratios from FOURIER directly. Instead the applicant derived hazard ratios per 1mmol/L reduction in LDL-C from the key secondary composite endpoint (MI, Stroke, CV death). The mean percentage reduction observed in the trial was applied to the modelled baseline LDL-C to obtain a predicted absolute reduction in LDL-C and this was used to adjust the hazard ratios per 1mmol/L reduction derived above to obtain the hazard ratios applied in the model. The NCPE made a number of changes to the model including removing the discontinuations rates applied and updating non-CV mortality rates applied. Due to the uncertainty regarding the treatment effect, the NCPE presented two treatment effect scenarios, one where treatment effects from FOURIER were applied directly and another where individual endpoints were adjusted for baseline LDL-C from FOURIER and a delayed mortality treatment effect was applied based on the CTTC meta-analysis.

Results

Incremental cost-effective ratios (ICERS) under the NCPE preferred scenarios and the applicant scenarios are presented in Table 1. All were above a cost-effectiveness threshold of €45,000/QALY.

Table 1Evolocumab ICERs vs no Treatment under NCPE and applicant assumptions

	NCPE Base Case Scenario 1 FOURIER Direct			NCPE Base case Scenario 2 LDL-C FOURIER and delayed CTTC Mortality			Applicant Base case		
	Incremental Cost	Incremental QALY	ICER	Incremental Cost	Incremental QALY	ICER	Incremental Cost	Incremental QALY	ICER
ASCVD – SP and HeFH- SP with LDL-C ≥4mmol/L	€55,265	0.06	€908,315	€58,121	0.28	€207,617	€51,176	0.53	€96,717
HeFH – PP with LDL-C 5mmol/L	€88,858	0.10	€920,507	€92,796	0.52	€177,146	€68,619	0.57	€120,909

ASCVD, Atherosclerotic Cardiovascular Disease Secondary Prevention –SP CTTC, Cholesterol Treatment Trialists Collaboration; HeFH- PP, Heterozygous Familial Hypercholesterolemia Primary Prevention; HeFH-SP, Heterozygous Familial Hypercholesterolemia –SP Secondary Prevention; ICER, Incremental Cost-effectiveness Ratio; LDL-C, Low Density Lipoprotein Cholesterol, mmol/L, millimole per Litre, QALY, Quality Adjusted Life Year

Sensitivity Analysis

One-way sensitivity and scenario analyses indicated that the ICER was sensitive to the baseline risk, effect of LDL-C lowering on event rates, CV history. The ICER was extremely sensitive to the CV mortality treatment effect applied and this is responsible for the majority of the difference between NCPE and applicant estimates. Using the actual observed event rates and population characteristics of the ASCVD population >4mmol/L increased the ICER by 46% using NCPE scenario 2 assumptions. Due to the way the model was programmed,

the NCPE were unable to run probabilistic sensitivity analysis for either of the NCPE preferred scenarios. Given the high ICERs, the NCPE estimate that the probability that evolocumab is cost effective at thresholds of €45,000 or €20,000 is zero.

4. Budget impact of evolocumab

The proposed ex-manufacturer price of evolocumab is €440.23 per pack (2x140mg 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 High Tech Drug Scheme including 8% wholesale mark-up, 5.25% rebate, VAT and high-tech patient care fee is €8,046.33. Based on a LDL-C treatment threshold of 4mmol/L for secondary ASCVD and 5mmol/L for HeFH primary prevention the NCPE project a gross budget impact of €2.9million in year 1 rising to €14.8million in year 5; cumulative 5 year gross budget impact of €44.4million. These estimates assume 50% of the entire PCSK9 inhibitor market share. If evolocumab claimed 100% of the PCSK9 market share the cumulative 5 year gross budget impact would be €88.8 million The net budget impact is expected to be equivalent to the gross budget impact given that evolocumab is an add on treatment.

5. Patient submission

No patient submissions were received.

6. Conclusion

The NCPE assessment of evolocumab has demonstrated the ability of evolocumab to reduce the risk of myocardial infarction and stroke. A reduction in the risk of cardiovascular mortality is clinically plausible given the ability of evolocumab to reduce LDL-C. However the magnitude of benefit is very uncertain (if present) as no evidence of mortality benefit was observed in the pivotal clinical trial FOURIER. There is a very low probability of cost-effectiveness and a high probability that the ICER far exceeds the cost-effectiveness threshold for existing treatments even when assuming a reasonable mortality benefit. The NCPE recommends that evolocumab not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.