New Medicine Recommendation

Evolocumab (Repatha SureClick®)

For prevention of cardiac events in patients with CHD and a history of ACS, in combination with a statin

Recommendation: Black

Evolocumab is not recommended for prevention of cardiac events in patients with CHD and a history of ACS, in combination with a statin.

The evidence for evolocumab in the setting of patients with CHD and a history of ACS, in combination with a statin was reviewed however this did not provide adequate cost effectiveness data to allow use in patients in addition to those covered by NICE TA394.

Summary of supporting evidence

Strengths

- Fourier study was a large 27,564 patient, multi region placebo controlled trial
- At 48 weeks, in the pivotal study the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59% P<0.001, for a mean absolute reduction of 1.45 mmol per litre, to a median of 0.78 mmol per litre.
- The primary end point (cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation) occurred in 1344 patients (9.8%) in the evolocumab group and in 1563 patients (11.3%) in the placebo group (hazard ratio, 0.85; 95% CI, 0.79 to 0.92; P<0.001).
- The key secondary end point (composite of cardiovascular death, myocardial infarction, or stroke) occurred in 816 patients (5.9%) in the evolocumab group and in 1013 patients (7.4%) in the placebo group (hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001).

Weaknesses

- Only one pivotal study
- Evolocumab had no observed effect on cardiovascular mortality, and P values for other outcomes should be considered exploratory.
- Given the findings of the FOURIER trial, in patients at high cardiovascular risk in whom low-density lipoprotein (LDL) cholesterol goals cannot be achieved despite the use of lipid-lowering treatment, it would be more cost-effective to add evolocumab to a high-intensity statin combined with ezetimibe, as needed and if this combination has an acceptable side-effect profile. These recommendations are consistent with current guidelines that were published after PCSK9 inhibitors became available.[1,2,3]
- There was one inconsistency in the trial results: a total of 17,335 patients from Europe (63% of the enrolled population) derived a lesser benefit from evolocumab on the key secondary composite end point of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.90; 95% confidence interval [CI], 0.80 to 1.01) than patients from North America (hazard ratio, 0.62; 95% CI, 0.51 to 0.76) (P = 0.01 for the interaction).

Details of Review

Name of medicine: Evolocumab (Repatha SureClick®)

Strength and form:

140 mg solution for injection in pre-filled syringe

140 mg solution for injection in pre-filled pen

420 mg solution for injection in cartridge

Dose and administration: Prior to initiating Repatha (evolocumab), secondary causes of hyperlipidaemia or mixed dyslipidaemia (e.g., nephrotic syndrome, hypothyroidism) should be excluded.

Primary hypercholesterolaemia and mixed dyslipidaemia in adults

The recommended dose of Repatha (evolocumab) is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

Homozygous familial hypercholesterolaemia in adults and adolescents aged 12 years and over

The initial recommended dose is 420 mg once monthly. After 12 weeks of treatment, dose frequency can be up-titrated to 420 mg once every 2 weeks if a clinically meaningful response is not achieved. Patients on apheresis may initiate treatment with 420 mg every two weeks to correspond with their apheresis schedule.

Established atherosclerotic cardiovascular disease in adults

The recommended dose of Repatha (evolocumab) is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

Patients with renal impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment, see section 4.4 for patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2).

Patients with hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment, see section 4.4 for patients with moderate and severe hepatic impairment.

Elderly patients (age ≥ 65 years)

No dose adjustment is necessary in elderly patients.

Paediatric population

The safety and efficacy of Repatha (evolocumab) in children aged less than 18 years has not been established in the indication for primary hypercholesterolaemia and mixed dyslipidaemia. No data are available.

The safety and efficacy of Repatha (evolocumab) in children aged less than 12 years has not been established in the indication for homozygous familial hypercholesterolaemia. No data are available.

Method of administration

Subcutaneous use.

Repatha (evolocumab) is for subcutaneous injection into the abdomen, thigh or upper arm region. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red, or hard. Repatha must not be administered intravenously or intramuscularly.

Repatha (evolocumab) 140 mg solution for injection in pre-filled syringe

The 140 mg dose should be delivered using a single pre-filled syringe. The 420 mg dose should be delivered using three pre-filled syringes administered consecutively within 30 minutes.

Repatha (evolocumab) 140 mg solution for injection in pre-filled pen

The 140 mg dose should be delivered using a single pre-filled pen. The 420 mg dose should be delivered using three pre-filled pens administered consecutively within 30 minutes.

Repatha (evolocumab) 420 mg solution for injection in cartridge

The 420 mg dose should be delivered using a single cartridge with the automated mini-doser.

Repatha (evolocumab) is intended for patient self-administration after proper training. Administration of Repatha (evolocumab) can also be performed by an individual who has been trained to administer the product.[4]

BNF therapeutic class / mode of action: Chapter 2.12 Lipid regulating drugs

Evolocumab binds selectively to PCSK9 and prevents circulating PCSK9 from binding to the low density lipoprotein receptor (LDLR) on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. Increasing liver LDLR levels results in associated reductions in serum LDL-cholesterol (LDL-C).[4]

Licensed indications:

Hypercholesterolaemia and mixed dyslipidaemia

Evolocumab is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- 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 a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Homozygous familial hypercholesterolaemia

Evolocumab is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

Established atherosclerotic cardiovascular disease

Evolocumab is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.[4]

Proposed use: Established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or,

- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

Clinical Evidence

Introduction

Despite major advances in the treatment of patients with atherosclerotic cardiovascular disease, substantial risk of recurrent cardiac events, stroke events, and cardiovascular death remains as well as high disease burden affecting quality of life and costs.[5,6,7] Lowering low-density lipoprotein (LDL) cholesterol levels with certain therapies, including statins, reduces cardiovascular events.[8,9] Many patients with established atherosclerotic cardiovascular disease need further LDL cholesterol lowering and remain at substantial risk for cardiovascular events despite optimal statin therapy.[5,9,10]

Evolocumab, a fully human monoclonal antibody inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9), lowers LDL cholesterol by approximately 60%.[11,12,13,14]

Pivotal Study

The evolocumab cardiovascular outcomes trial FOURIER, was a randomized, double-blind, placebo-controlled study including 27,564 patients with prior myocardial infarction (MI), non-haemorrhagic stroke, or symptomatic peripheral artery disease, as well as additional characteristics that placed them at higher cardiovascular risk.[a] Patients were between 40 and 86 years of age and had to have a fasting LDL cholesterol level of 1.8 mmol per litre or higher or a non–high-density lipoprotein (HDL) cholesterol level of 2.6 mmol per litre or higher while they were taking an optimised regimen of lipid-lowering therapy, which was defined as preferably a high-intensity statin but must have been at least atorvastatin at a dose of 20 mg daily or its equivalent, with or without ezetimibe. Over 99% of patients were on moderate to high intensity statin and at least one other cardiovascular medicine.[15,16]

Patients were randomized to receive (either 140 mg every 2 weeks or 420 mg every month, according to patient preference) or matching placebo. The median duration of follow-up was 26 months.

The primary efficacy end point was major cardiovascular events, defined as the composite of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularization. The key secondary efficacy end point was the composite of cardiovascular death, myocardial infarction, or stroke.

The median LDL cholesterol level at baseline was 2.4 mmol per litre. At 48 weeks, the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59% P<0.001, for a mean absolute reduction of 1.45 mmol per litre, to a median of 0.78 mmol per litre. At 48 weeks in the evolocumab group, the LDL cholesterol level was reduced to 1.8 mmol per litre or lower in 87% of the patients, to 1.0 mmol per litre or lower in 67% of the patients, and to 0.65 mmol per litre or lower in 42% of the patients, as compared with 18%, 0.5%, and less than 0.1%, respectively, of the patients in the placebo group (P<0.001 for all comparisons of evolocumab vs. placebo).

The primary end point[b] occurred in 1344 patients (9.8%) in the evolocumab group and in 1563 patients (11.3%) in the placebo group (hazard ratio, 0.85; 95% CI, 0.79 to 0.92; P<0.001). The

[a] Including one major and two minor criteria - 80% had hypertension, 36% had diabetes mellitus, and 28% were daily smokers

[b] Cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization

key secondary end point[c] occurred in 816 patients (5.9%) in the evolocumab group and in 1013 patients (7.4%) in the placebo group (hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001). Evolocumab had no observed effect on cardiovascular mortality, and P values for other outcomes should be considered exploratory.

Risk reduction with regard to the primary end point was 12% in the first year and 19% beyond the first year. The key secondary end point risk reduction was 16% in the first year and 25% beyond the first year. There were reductions of 21% to 27% in the risk of myocardial infarction, stroke, and coronary revascularization but no observed effect on the rates of hospitalization for unstable angina, cardiovascular death or hospitalization for worsening heart failure, or death from any cause.

The effects were consistent across quartiles of baseline LDL cholesterol levels, from patients in the top quartile, who had a median LDL cholesterol level of 3.3 mmol per litre at baseline, down to those in the lowest quartile, who had a median LDL cholesterol level of 1.9 mmol per litre at baseline. The efficacy of evolocumab was also consistent across levels of intensity of statin therapy, regardless of ezetimibe use.

There was one inconsistency in the trial results: a total of 17,335 patients from Europe (63% of the enrolled population) derived a lesser benefit from evolocumab on the key secondary composite end point of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.90; 95% confidence interval [CI], 0.80 to 1.01) than patients from North America (hazard ratio, 0.62; 95% CI, 0.51 to 0.76) (P = 0.01 for the interaction). The trial report does not expand on this anomaly.[17]

Safety

No significant between-group differences were seen in the overall rates of adverse events, serious adverse events, or adverse events thought to be related to the study agent and leading to discontinuation of the study regimen. Injection-site reactions were more frequent with evolocumab (2.1% vs. 1.6%). Around 90% of adverse reactions were mild in each group. The rates of adjudicated cases of new-onset diabetes did not differ significantly between the two groups (hazard ratio, 1.05; 95% CI, 0.94 to 1.17). New binding antibodies developed in 43 evolocumab treated patients (0.3%), and development of neutralizing antibodies did not occur in any patient.

Table Adverse Drug Reactions in FOURIER trial

[c] Composite of cardiovascular death, myocardial infarction, or stroke

Outcome	Evolocumab (N=13,769)	Placebo (N=13,756)
Adverse events — no. of patients (%)		
Any	10,664 (77.4)	10,644 (77.4)
Serious	3410 (24.8)	3404 (24.7)
Thought to be related to the study agent and leading to discontinuation of study regimen	226 (1.6)	201 (1.5)
Injection-site reaction*	296 (2.1)	219 (1.6)
Allergic reaction	420 (3.1)	393 (2.9)
Muscle-related event	682 (5.0)	656 (4.8)
Rhabdomyolysis	8 (0.1)	11 (0.1)
Cataract	228 (1.7)	242 (1.8)
Adjudicated case of new-onset diabetes†	677 (8.1)	644 (7.7)
Neurocognitive event	217 (1.6)	202 (1.5)
Laboratory results — no. of patients/total no. (%)		
Aminotransferase level >3 times the upper limit of the normal range	240/13,543 (1.8)	242/13,523 (1.8)
Creatine kinase level >5 times the upper limit of the normal range	95/13,543 (0.7)	99/13,523 (0.7)

* The between-group difference was nominally significant (P<0.001).
† The total numbers of patients were 8337 in the evolocumab group and 8339 in the placebo group, because patients with prevalent diabetes at the start of the trial were excluded.

Discussion

Evolocumab has been shown to reliably lower cholesterol levels in patients and has met its primary and secondary endpoints thereby demonstrating its efficacy in preventing cardiovascular events. Similar results have been shown when cholesterol levels have been lowered using other agents, for example by using intensive statin dosing. The Cholesterol Treatment Trialists' (CTT) Collaboration analysed data from 170 000 participants in 26 randomised trials to assess the safety and efficacy of more intensive lowering of LDL cholesterol with statin therapy.

In the trials of more versus less intensive statin therapy, the weighted mean further reduction in LDL cholesterol at 1 year was 0·51 mmol/L. Compared with less intensive regimens, more intensive regimens produced a highly significant 15% (95% CI 11–18; p<0·0001) further reduction in major vascular events, consisting of separately significant reductions in coronary death or non-fatal myocardial infarction of 13% (95% CI 7–19;p<0·0001), in coronary revascularisation of 19% (95% CI 15–24; p<0·0001), and in ischaemic stroke of 16% (95% CI 5–26; p=0·005). Per 1·0 mmol/L reduction in LDL cholesterol, these further reductions in risk were similar to the proportional reductions in the trials of statin versus control.

When both types of trial were combined, similar proportional reductions in major vascular events per 1·0 mmol/L LDL cholesterol reduction were found in all types of patient studied (rate ratio [RR] 0·78, 95% CI 0·76–0·80; p<0·0001), including those with LDL cholesterol lower than 2 mmol/L on the less intensive or control regimen. Across all 26 trials, all-cause mortality was reduced by 10% per 1·0 mmol/L LDL reduction (RR 0·90, 95% CI 0·87–0·93; p<0·0001), largely reflecting significant reductions in deaths due to coronary heart disease (RR 0·80, 99% CI 0·74–0·87; p<0·0001) and other cardiac causes (RR 0·89, 99% CI 0·81–0·98; p=0·002), with no significant effect on deaths due to stroke (RR 0·96, 95% CI 0·84–1·09; p=0·5) or other vascular causes (RR 0·98, 99% CI 0·81–1·18; p=0·8).[18]

Evolocumab is a relatively expensive option for reducing cholesterol levels and is a relatively new agent with many fewer clinical studies then there are for statins. A new England Journal of Medicine paper focusing on evolocumab and clinical outcomes in patients with cardiovascular disease makes the following salient points:

- Overall, 74 patients would need to be treated over a period of 2 years to prevent a cardiovascular death, myocardial infarction, or stroke.
- The magnitude of benefit of evolocumab in reducing the risk of major coronary events, stroke, and urgent coronary revascularization is largely consistent with the benefit seen with statins on a per–millimole-per-litre basis of LDL cholesterol lowering.
- In the FOURIER trial, inhibition of PCSK9 with evolocumab on a background of statin therapy lowered LDL cholesterol levels to a median of 0.78 mmol per litre and reduced the risk of cardiovascular events.
- These findings show that patients with atherosclerotic cardiovascular disease benefit from lowering of LDL cholesterol levels below current targets.[16]

The outcomes in the FOURIER trial were similar to the outcomes found in the IMPROVE-IT study which added ezetimibe to statin therapy in patients with acute coronary syndromes. The primary efficacy end point was a composite of death from cardiovascular disease, a major coronary event (nonfatal myocardial infarction, documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization), or nonfatal stroke. There was a 24% further lowering of LDL cholesterol level when ezetimibe was combined with simvastatin and an absolute risk reduction of 2.0 percentage points for the primary end point.[19]

The trial results do not fully accord with the CTT meta-analysis, which would have predicted a 30-35% decrease in events based on the LDL reduction in the trial – the results from FOURIER are approximately 50% of those predicted by CTT.[18]

Safety Summary

The SPC for Evolocumab (Repatha SureClick®) lists the following adverse events:[4]

Incidence of Event	Adverse Event
Very Common (≥1/10)	
Common (≥1/100 to <1/10)	Influenza, Nasopharyngitis, Upper respiratory tract infection, Rash, Nausea, Back pain, Arthralgia, Injection site reactions[1]
Uncommon (≥1/1,000 to <1/100)	Urticaria
Rare (≥1/10,000 to <1/1,000)	

[1] Injection site reactions: The most frequent injection site reactions were injection site bruising, erythema, haemorrhage, injection site pain, and swelling

Cost Effectiveness Summary

Cost Effectiveness Review

The cost effectiveness of adding evolocumab to statin therapy in patients with atherosclerotic cardiovascular disease, substantial risk of recurrent cardiac events, stroke events, and cardiovascular death has been analysed in a JAMA Cardiology article[20] and its supplement.[21]

In the base case, using US clinical practice patients with atherosclerotic cardiovascular disease with low-density lipoprotein cholesterol levels of at least 70 mg/dL (1.81mmol/litre (to convert to millimoles per litre, multiply by 0.0259)) and an annual events rate of 6.4 per 100 patient-years,

evolocumab was associated with increased cost and improved QALY: incremental cost, $105 398 (£78,524[d]); incremental QALY, 0.39, with an ICER of $268 637 (£200,142) per QALY gained ($165 689 (£123,443) with discounted price of $10 311 (£7,682) based on mean rebate of 29% for branded pharmaceuticals).[20]

Sensitivity and scenario analyses demonstrated ICERs ranging from $100 193 to $488 642 per QALY (£74,647 to £364,053) with ICER of $413 579 (£308,128) per QALY for trial patient characteristics and event rate of 4.2 per 100 patient-years ($270,192 (£201,301) with discounted price of $10 311 (£7,682) and $483 800 (£360,444) (if no cardiovascular mortality reduction emerges. Evolocumab treatment exceeded $150 000 (£111,754) per QALY in most scenarios but would meet this threshold at an annual net price of $9669 (£7,204) ($6780 (£5,051) (for the trial participants) or with the discounted net price of $10 311 (£7,682) in patients with low-density lipoprotein cholesterol levels of at least 80 mg/dL.[20]

The study used a QALY of $150,000 as acceptable and did not calculate that evolocumab could meet this standard at its US cost of $9669 for a year's treatment. In the UK, the cost for a year's treatment with evolocumab using monthly dosing schedule is £4,082.40 ($5,438.49), which may produce a QALY less than the $150,000 standard used in the US but does not meet the UK/NICE accepted maximum cost per QALY level of £20,000 to £30,000 per QALY.[22,23]

Relevant Guidance

NICE

NICE TA394 has approved evolocumab is recommended as an option for treating primary hypercholesterolaemia or mixed dyslipidaemia, only if:

- The dosage is 140 mg every 2 weeks.
- Low-density lipoprotein concentrations are persistently above the thresholds specified in table 1 despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached, or further titration is limited by intolerance (as defined in NICE's guideline on familial hypercholesterolaemia).
- The company provides evolocumab with the discount agreed in the patient access scheme.[24]

Table 1 Low-density lipoprotein cholesterol concentrations above which evolocumab is recommended

	Without CVD	With CVD	
		High risk of CVD[1]	Very high risk of CVD[2]
Primary non-familial hypercholesterolaemia or mixed dyslipidaemia	Not recommended at any LDL-C concentration	Recommended only if LDL-C concentration is persistently above 4.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre
Primary heterozygous-familial hypercholesterolaemia	Recommended only if LDL-C concentration is persistently above 5.0 mmol/litre	Recommended only if LDL-C concentration is persistently above 3.5 mmol/litre	

[1] High risk of CVD is defined as a history of any of the following: acute coronary syndrome (such as myocardial infarction or unstable angina needing hospitalisation); coronary or other

[d] Dollar to pound conversions calculated using Microsoft calculator converter function 23 May 2018, 13.32 based on an exchange rate of 1.3317 US$ per UK£

arterial revascularisation procedures; coronary heart disease; ischaemic stroke; peripheral arterial disease.
[2] Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Strengths and Limitations of the Evidence

Strengths

- Fourier study was a large 27,564 patient, multi region placebo controlled trial
- At 48 weeks, in the pivotal study the least-squares mean percentage reduction in LDL cholesterol levels with evolocumab, as compared with placebo, was 59% P<0.001, for a mean absolute reduction of 1.45 mmol per litre, to a median of 0.78 mmol per litre.
- The primary end point (cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation) occurred in 1344 patients (9.8%) in the evolocumab group and in 1563 patients (11.3%) in the placebo group (hazard ratio, 0.85; 95% CI, 0.79 to 0.92; P<0.001).
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Weaknesses

- Only one pivotal study
- Evolocumab had no observed effect on cardiovascular mortality, and P values for other outcomes should be considered exploratory.
- Given the findings of the FOURIER trial, in patients at high cardiovascular risk in whom low-density lipoprotein (LDL) cholesterol goals cannot be achieved despite the use of lipid-lowering treatment, it would be more cost-effective to add evolocumab to a high-intensity statin combined with ezetimibe, as needed and if this combination has an acceptable side-effect profile. These recommendations are consistent with current guidelines that were published after PCSK9 inhibitors became available.
- There was one inconsistency in the trial results: a total of 17,335 patients from Europe (63% of the enrolled population) derived a lesser benefit from evolocumab on the key secondary composite end point of cardiovascular death, myocardial infarction, or stroke (hazard ratio, 0.90; 95% confidence interval [CI], 0.80 to 1.01) than patients from North America (hazard ratio, 0.62; 95% CI, 0.51 to 0.76) (P = 0.01 for the interaction).

Prescribing and risk management issues:

Evolocumab is administered as a subcutaneous injection.

Commissioning Considerations

Comparative Unit Costs

Drug	Example regimen	Pack cost	Cost per patient per year
Evolocumab (Repatha)	140mg/ml soln. for inj. Prefilled syringe, 1 x 1ml 1 injection every 2 weeks	£170.10[25]	£4,448.60
Evolocumab (Repatha)	420mg/ml soln. for inj. Solution for injection in cartridge, 1 x 3.5ml 1 injection every month	£340.20[25]	£4,082.40

Drug	Example regimen	Pack cost	Cost per patient per year
Ezetimibe 10mg tablets	One tablet each day (10mg)	£26.31 (28)[26]	£342.03
Additional 40mg atorvastatin tablet	One 40mg tablet each day in patient already taking atorvastatin 40mg daily (equivalent to total 80mg dose)[e]	£0.98 (28)[26]	£12.74
Costs based on MIMS online May 2018 and the Drug Tariff online, May 2018, excluding administration costs and VAT.			

Associated additional costs or available discounts:

NICE TA394 included a national patient access scheme. It is not clear if this would apply to indications not covered by TA394 therefore list prices have been used in this appraisal.

Productivity, service delivery, implementation:

Initiation would need to take place in secondary care outpatient setting.

Anticipated Patient Numbers and Budget Impact

NICE TA394 models essentially the same population as the Amber0 population in this review. This estimated around 6 per 100,000 population will be eligible in year 1, rising to 26 per 100,000 in year 5

For Lancashire, with an estimated population of around 1.5 million, the estimated acquisition costs for evolocumab in in patients with CHD and a history of ACS will be:

Year 1: £367,416

Year 5: £1,592,136

The above figures are based on using the monthly injection. The every 14 days injection will be around 10% more expensive.

Innovation, need, equity:

Evolocumab offers a new mechanism to lower cholesterol levels and can achieve the appropriate levels in patients who are already receiving maximum doses of statins and ezetimibe.

[e] Atorvastatin 80mg tablets cost £2.06 for 28, atorvastatin 40mg costs 98p for 28 therefore the most cost effective method of prescribing 80mg of atorvastatin is to prescribe 2 x 40mg tablets. Replacing the 40mg tablet with an 80mg tablet would incur a slight cost pressure of £1.30 per year.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: high quality randomised controlled trials (RCTs) with low risk of bias systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: clinical trials at moderate or high risk of bias systematic reviews or meta-analyses of such clinical trials or with inconsistent findings cohort studies case-control studies	
Level 3	Disease-oriented evidence, or evidence from: consensus guidelines expert opinion case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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