NICE TA implementation guidance – Alirocumab and evolocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia

Recommendation

The East Kent Prescribing Group have approved Alirocumab and evolocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia. It must be noted that referrals should be made to an endocrinologist.

Approved by: East Kent Prescribing Group *(Representing Ashford CCG, Canterbury and Coastal CCG, South Kent Coast CCG and Thanet CCG)*

Date: April 2017

Address: c/o *Canterbury and Coastal CCG, Ground Floor, Council Offices, Military Road, Canterbury, Kent,CT1 1YW*

Contact: T: 03000 425019 | E: accg.eastkentprescribing@nhs.net

NICE TA implementation guidance – Alirocumab and evolocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia

Purpose

Detail guidance supporting the implementation of NICE technology appraisal[1] (TA) 393 on alirocumab and TA394 on evolocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia (Appendix 1). This guidance has been developed to ensure the same criteria are applied to assess and initiate patients for treatment across Kent and Medway, and has been recommended by the Kent and Medway Policy Recommendation and Guidance Committee (PRGC).

What are hypercholesterolaemia and mixed dyslipidaemia?

Hypercholesterolaemia is the presence of high concentrations of cholesterol in the blood, typically including elevated low-density lipoprotein cholesterol (LDL-C). Primary hypercholesterolaemia is associated with an underlying genetic cause, which may be caused by a genetic defect (familial)[2], or more commonly, by the interaction of several genes with dietary and other factors such as smoking or physical inactivity (non-familial).

Mixed dyslipidaemia is defined as elevations in LDL-C and triglyceride levels that are often accompanied by low levels of high-density lipoprotein (HDL) cholesterol.

People with hypercholesterolaemia are at increased risk of cardiovascular disease (CVD) because long-term elevations of cholesterol accelerate the build-up of fatty deposits in the arteries (atherosclerosis). The narrowed arteries can cause diseases such as angina, myocardial infarction and stroke, particularly in familial hypercholesterolaemia.

How are primary hypercholesterolaemia and mixed dyslipidaemia currently managed?

The current management of primary hypercholesterolaemia and mixed dyslipidaemia involves dietary and lifestyle changes such as smoking cessation, weight loss and increased physical activity. NICE clinical guideline (CG) 181[3] on lipid modification to prevent

[1] Regulations require clinical commissioning groups (CCGs), NHS England and local authorities to comply with recommendations in a technology appraisal within 3 months of its date of publication.
[2] Most people with familial hypercholesterolaemia (FH) have inherited a defective gene for FH from only one parent and are therefore heterozygous. Rarely, a person will inherit a genetic defect from both parents and will have homozygous FH.
[3] Published July 2014; last updated September 2016.

cardiovascular disease and NICE CG71[4] on familial hypercholesterolaemia, recommend initial treatment with statins. NICE technology appraisal (TA) 385[5] on ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia (2016) recommends ezetimibe as an option for treating adults:

- as a monotherapy when statins are contraindicated or not tolerated, and
- in combination with statins when:
    - initial statin therapy does not provide appropriate control of serum total or LDL-C, or
    - a change from initial statin therapy to an alternative statin is being considered.

According to NICE CG71, LDL-lowering apheresis (a process similar to dialysis which removes low density lipoprotein from the blood stream) may be considered in exceptional instances for the treatment of people with heterozygous familial hypercholesterolaemia.

Who is responsible for commissioning services for hypercholesterolaemia?

NHS England is responsible for commissioning services for patients with homozygous familial hypercholesterolaemia; clinical commissioning groups (CCGs) are responsible for commissioning services for patients with heterozygous familial hypercholesterolaemia.

What are alirocumab and evolocumab?

Alirocumab (Praluent, Sanofi) and evolocumab (Repatha, Amgen) are monoclonal antibodies that inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9), thereby helping to lower levels of LDL-C in the blood. According to NICE they are generally regarded as being clinically equivalent (although this has not been confirmed by head-to-head trials). Both have marketing authorisation in the UK for treating adults with primary hypercholesterolaemia (heterozygous-familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin, or a statin plus 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 cannot tolerate or cannot be given statins.

Alirocumab and evolocumab are both given by subcutaneous injection.

---

[4] Published August 2008; last updated July 2016. Sections of this guideline are currently under review (i.e. strategies for identifying people with FH, scoring criteria to diagnose FH and the clinical and cost effectiveness of statins versus placebo); expected publication date is currently TBC.
[5] This guidance replaces NICE TA132 on ezetimibe (2007).

What does NICE say about alirocumab and evolocumab?

According to NICE TA393 on alirocumab (June 2016) and TA394 on evolocumab (June 2016), both of these agents are recommended as options for treating primary hypercholesterolaemia or mixed dyslipidaemia, but only if[6]:

- Low-density lipoprotein concentrations are persistently[7] 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[8]
- The companies provide them with the discounts agreed in the patient access schemes
- The dosage of evolocumab is 140mg every two weeks

Table 1 – LDL-C concentrations above which alirocumab and evolocumab are recommended by NICE

	Without CVD	With CVD	
		High risk of CVD[§]	Very high risk of CVD[‡]
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	

[§]High risk of CVD 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.
[‡]Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).
Abbreviations: CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

NICE noted in TA393 and TA394 that absolute statin intolerance is rare, accounting for less than 5% of the population, however up to 25% were currently reported to be intolerant of statins. The misidentification of people as being unable to tolerate statins may make subsequent treatments less cost-effectiveness. Consequently, NICE emphasised that its recommendations on alirocumab and evolocumab should only apply when the maximum

[6] This guidance is not intended to affect the position of patients whose treatment with alirocumab or evolocumab was started within the NHS before this guidance was published.
[7] In TA394, the committee note that 'persistent' LDL-C means on-treatment LDL-C concentrations confirmed by repeated measures. In Kent and Medway it has been agreed, in consultation with local consultant chemical pathologists, that LDL concentrations would be considered persistently high if there are two measured LDL levels above the thresholds specified by NICE despite maximally tolerated lipid lowering therapy; these need to be documented in the Blueteq forms requesting use of alirocumab and evolocumab.
[8] Defined by NICE as the presence of clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy.

tolerated lipid-lowering therapy has failed (i.e. either the maximum dose has been reached or further titration is limited by intolerance).

What do local clinicians think?

Comments from three consultant chemical pathologists (one each from Medway NHS Foundation Trust, Dartford and Gravesham NHS Trust and Maidstone and Tunbridge Wells NHS Trust) were incorporated into the guidance.

What will be the cost impact of implementing TA guidance on alirocumab and evolocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia?

Regulations require clinical commissioning groups, NHS England and local authorities to comply with recommendations in a technology appraisal within 3 months of its date of publication. NICE have developed combined resource impact tools to model the cost of implementing TA guidance on alirocumab and evolocumab.

Were any equality issues identified?

No. See Appendix 2 for more information.

This briefing note was completed by the South East CSU, Medicines Management team in January 2017.

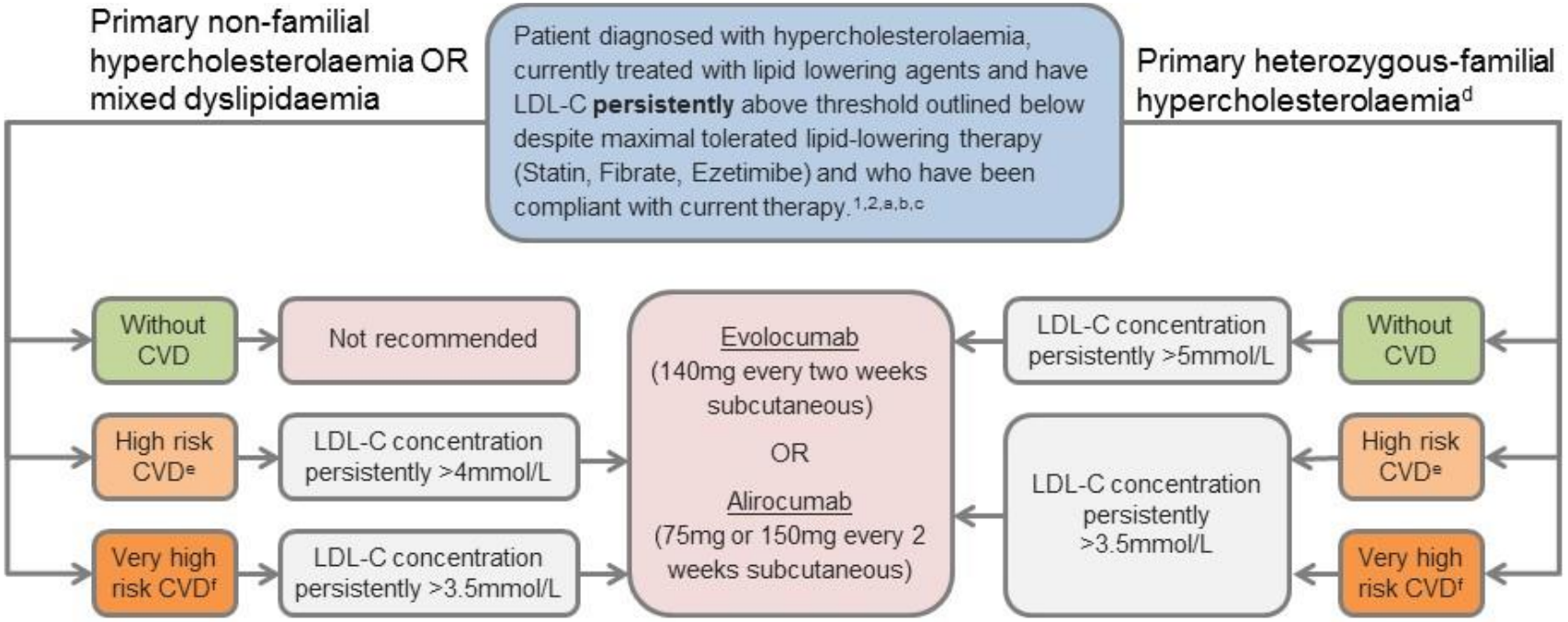
Contact for further information:

Medicines Management team

South East CSU

Email: KMCS.HCD@nhs.net

Appendix 1 – TA implementation guidance: Alirocumab and evolocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia



[a] Evolocumab and alirocumab can be used:
- In combination with a statin, or a statin plus other lipid-lowering therapies in patients unable to reach LDL-C goals with maximum tolerated dose of a statin or,
- Alone or in combination with other lipid-lowering therapies in patients who cannot tolerate or cannot be given statins.

[b] Absolute statin intolerance is rare, accounting for <5% of people. Misidentification of people as being unable to tolerate statins may worsen the cost-effectiveness of subsequent treatments.

[c] In TA394, the committee note that 'persistent' LDL-C means on-treatment LDL-C concentrations confirmed by repeated measures. In Kent and Medway it has been agreed, in consultation with local consultant chemical pathologists, that LDL concentrations would be considered persistently high if there are two measured LDL levels above the thresholds specified by NICE despite maximally tolerated lipid lowering therapy; these need to be documented in the Blueteq forms requesting use of alirocumab and evolocumab.

[d] Homozygous-familial hypercholesterolaemia (HoFH) is not within the marketing authorisation of alirocumab and evolocumab, and not covered by NICE TA guidance on these agents (i.e. TA393 and TA394). NHS England is responsible for commissioning services for patients with HoFH.

[e] 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 arterial revascularisation procedures; chronic heart disease; ischaemic stroke; peripheral arterial disease.

[f] Very high risk of CVD is defined as recurrent cardiovascular events or cardiovascular events in more than 1 vascular bed (that is, polyvascular disease).

Abbreviations: CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

References: (1) NICE TA393 *Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia* (2016). (2) NICE TA394 *Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia* (2016).

Appendix 2 – Equality analysis screening tool

Date of assessment	4 January 2017
Assessor name	Kent and Medway Policy Recommendation and Guidance Committee (PRGC)
Name of the policy, function, service development	NICE TA implementation guidance – Alirocumab and evolocumab for the treatment of primary hypercholesterolaemia and mixed dyslipidaemia
Aim/Purpose of the policy, function, service development	Support implementation of NICE TA393 and TA394 across Kent and Medway.

1. Do you consider the policy/function/service development to have an *adverse equality impact / health inequality impact* on any of the protected groups as defined by the Equality Act 2010? Write either 'yes' or 'no' next to the appropriate group(s)

Protected Group	Yes or No	Protected Group	Yes or No	Protected Group	Yes or No
Age	No	Gender reassignment	No	Marriage/ Civil Partnership (employment matters)	No
Disability	No	Pregnancy/maternity	No	Religion/belief	No
Gender	No	Race	No	Sexual orientation	No

2. If you answered 'yes' to any of the above, give your reasons why

–

3. If you answered 'no' to any of the above, give your reasons why

Disability: During development of NICE TA394 on evolocumab, clinical experts noted that community nursing support will be needed if patients cannot self-inject. **Religion/belief and race:** During development of NICE TA393 on alirocumab, clinical experts noted that alirocumab is an injection only treatment, which will exclude people who will not accept injection based therapies, including many from ethnic minority groups. It was also noted that the incidence of familial hypercholesterolaemia could be higher in people of Ashkenazi Jewish origin. The NICE TA implementation guidance detailed in this document is consistent with recommendations in TA393 and TA394. Regulations require CCGs, NHS England and local authorities to comply with recommendations in a TA within 3 months of its date of publication. There was no indication during development of this guidance that there is likely to be an adverse equality impact/ health inequality impact on any of the protected groups as defined by the Equality Act 2010.

4. Please indicate if a Full Equality Analysis is recommended		NO ✓	YES
Signature of Project Lead 	Date completed 19/01/2017	**IF YES, BEGIN TO GATHER DATA FOR COMPLETION OF A FULL EQUALITY ANALYSIS**	
Signature of reviewing CCG Equality and Diversity Lead	Date reviewed		