Evidence Review for Prescribing Clinical Network

Treatment: Lomitapide (Lojuxta®) for Homozygous Familial Hypercholesterolaemia (HoFH) in adult patients

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Summary page

How strong is the evidence for claimed efficacy? - Phase III, open label study RCT

Potential advantages in terms of: efficacy, compliance, pharmacokinetics, drug interactions and adverse effects? Lomitapide is an orally administered first-in-class small-molecule inhibitor of microsomal triglyceride transfer protein (MTP). One small phase III single-arm open-label study suggest that lomitapide is an effective treatment, when compared with standard therapy. However, assessing lomitapide's place in therapy in the NHS is problematic due to the small cohort of patients eligible to be treated with this new therapy.

Is there a clear place in therapy / treatment pathway? No
Is monitoring for efficacy required? Yes
Is monitoring for toxicity required? Yes
Is dose titration required? Yes
Traffic light status – Red or Black
Role of the specialist – Yes; specialist input required
Role of GP: N/A

Financial implications: Annual cost of £230K per patient per year.

National Guidance available

NICE
Currently awaiting guidance – no date given.

Scottish Medicines Consortium (SMC) – 10th February 2014
Not recommended.

All Wales Medicines Strategy Group (AWMSG) - 6th December 2013
Not recommended.

Recommendations:

Lomitapide may be an option for prescribing by specialists for the treatment of patients with Homozygous Familial hypercholesterolaemia in adult patients who have not responded to conventional treatment lipid lowering treatments; noting that substantial increases in liver fat content and transient elevations of liver enzymes have been observed. Comparative assessments against statins and other therapies for managing HoFH are not available and longer term safety data are lacking, so the appropriate place of lomitapide in therapy is uncertain and national guidance from Scotland and Wales do not recommend its use.

CCGs need to decide if they wish to commission lomitapide for the financial year 2014/15. NHSE is expected to commission from April 2015.

PCN recommendation:
Black listed - Not routinely recommended for prescribing.

1. Purpose of the Review

On 30 May 2013 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Lojuxta, 5mg, 10mg, 20mg hard capsules intended as an adjunct to a low fat diet and other lipid lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

Lomitapide is a microsomal triglyceride transfer protein inhibitor (first in class) given orally once daily.

Local decision makers will need to consider the place of lomitapide alongside existing treatments.

2. Appropriateness

2.1 The patient:
Adult patients with homozygous familial hypercholesterolaemia.

2.2 The problem:

Definition:
In some people, a high cholesterol concentration in the blood is caused by an inherited genetic defect known as familial hypercholesterolaemia (FH). A raised cholesterol concentration in the blood is present from birth and may lead to early development of atherosclerosis and coronary heart disease. The disease shows an autosomal dominant pattern of inheritance, being transmitted from generation to generation in such a way that siblings and children of a person with FH have a 50% risk of inheriting FH.

Most people with 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 or compound heterozygous FH.

and prognosis: Homozygous FH is rare, with symptoms appearing in childhood, and is associated with early death from coronary heart disease. Homozygous FH has an incidence of approximately one case per one million.

Etiology

Diagnosis: (from NICE CG71 Identification and management of familial hypercholesterolaemia)
A family history of premature coronary heart disease should always be assessed in a person being considered for a diagnosis of FH.
Coronary heart disease risk estimation tools such as those based on the Framingham algorithm should not be used because people with FH are already at a high risk of premature coronary heart disease.
Healthcare professionals should offer all people with FH a referral to a specialist with expertise in FH for confirmation of diagnosis and initiation of cascade testing (see appendix D of NICE CG71).
Cascade testing using a combination of DNA testing and LDL-C concentration measurement is recommended to identify affected relatives of those index individuals with a clinical diagnosis of FH. This should include at least the first- and second- and, when possible, third-degree biological relatives. The use of a nationwide, family-based, follow-up system is recommended to enable comprehensive identification of people affected by FH.

2.3 The Intervention:

Lomitapide may be an option for patients with homozygous familial hypercholesterolaemia (HoFH) with an inadequate response to current therapy. It is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with HoFH. It is a microsomal triglyceride transfer protein inhibitor (first in class) given orally once daily.

Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolemia (e.g. nephrotic syndrome, hypothyroidism) must be excluded.
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How does it work:
Lomitapide is a novel microsomal triglyceride transfer protein (MTP) inhibitor, which reduces both plasma low density lipoprotein (LDL) and triglycerides (TG). MTP transfers TG on to apolipoprotein B within the liver during the assembly of very low density lipoproteins (VLDL), the precursor to LDL. In the absence of MTP, the liver cannot secrete VLDL, leading to the absence of all lipoproteins containing apolipoprotein B in the plasma. Inhibition of MTP therefore reduces LDL production and LDL cholesterol (LDL-C) levels.

Care setting: It is proposed that treatment with lomitapide should be initiated and monitored by a physician experienced in the treatment of lipid disorders.

Frequency (Dose)

The recommended starting dose is 5 mg once daily. After 2 weeks the dose may be increased, based on acceptable safety and tolerability, to 10 mg and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and to the maximum recommended dose of 60 mg.

The dose should be escalated gradually to minimise the incidence and severity of gastrointestinal side effects and aminotransferase elevations.

Administration with food may increase exposure to lomitapide; it should be taken on an empty stomach, at least 2 hours after the evening meal because the fat content of a recent meal may adversely impact gastrointestinal tolerability.

With concomitant weak inhibitors of cytochrome P450 enzyme CYP3A4 (e.g. cimetidine, ranolazine, and fosaprepitant), reduce lomitapide dose to 5 mg once daily (if taking less than 40 mg once daily), or to 10 mg once daily (if taking 40–60 mg once daily), then adjust as necessary.

2.4 Alternative treatments:

Management of FH aims to reduce LDL levels and cardiovascular risk with a combination of:
• Dietary and lifestyle changes – smoking cessation, dietary manipulation, weight loss and increased physical activity.
• Lipid modifying therapy:
    o Statins and high intensity statins
    o Ezetimibe
    o Bile acid sequestrant e.g. colestyramine
    o Nicotinic acid
    o Fibrate e.g. bezafibrate and gemfibrozil
• LDL apheresis
• Other therapies e.g. blood pressure lowering drugs, low dose aspirin and management of comorbidities such as diabetes.

Liver transplantation may be considered if there is disease progression despite treatment with lipid-modifying medication and LDL apheresis.

3. Effectiveness

3.1 Expected benefits
In an open-label Phase III study (n=29), the addition of lomitapide combined with a low-fat diet to standard therapy (with or without apheresis) was associated with a mean reduction from baseline in LDL cholesterol of 50% at 26 weeks (primary outcome), 44% at 56-weeks and 38% at 78-weeks ($p<0.01$ for all comparisons vs. baseline).

3.2 Is there a plausible biological basis for effectiveness?

Lomitapide is an orally administered first-in-class small-molecule inhibitor of microsomal triglyceride transfer protein (MTP), an intracellular enzyme critical to the assembly of apolipoprotein B (apoB)-containing lipoproteins in enterocytes and hepatocytes. Inhibition of MTP prevents the synthesis of chylomicrons and very-low-density lipoprotein (VLDL), which are

precursors to the atherogenic low-density lipoprotein (LDL) particle. The proposed indication for lomitapide is to reduce LDL-cholesterol (LDL-C), total cholesterol (TC), apoB, and triglycerides (TG) in patients with homozygous familial hypercholesterolemia.

Although statins are the pharmacological agents of choice, individuals with HoFH have absent or dysfunctional LDL-receptors (LDL-R), which substantially attenuates the efficacy of statins.

3.3 Side-effects/complications

Lomitapide can cause elevations in alanine aminotransferase [ALT] and aspartate aminotransferase [AST] and hepatic steatosis. The extent to which lomitapide-associated hepatic steatosis promotes the elevations in aminotransferase is unknown. Although cases of hepatic dysfunction (elevated aminotransferase with increase in bilirubin or International Normalized Ratio [INR]) or hepatic failure have not been reported, there is concern that lomitapide could induce steatohepatitis, which can progress to cirrhosis over several years. The clinical studies supporting the safety and efficacy of lomitapide in HoFH would have been unlikely to detect this adverse outcome given their size and duration.

Measure ALT, AST, alkaline phosphatase, total bilirubin, gamma-glutamyl transferase (gamma-GT) and serum albumin before initiation of treatment with Lojuxta. The medicinal product is contraindicated in patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests. If the baseline liver-related tests are abnormal, consider initiating the medicinal product after appropriate investigation by a hepatologist and the baseline abnormalities are explained or resolved.

During the first year, measure liver-related tests (ALT and AST, at a minimum) prior to each increase in dose or monthly, whichever occurs first. After the first year, do these tests at least every 3 months and before any increase in dose. Decrease the dose of Lojuxta if elevations of aminotransferase are observed and discontinue treatment for persistent or clinically significant elevations.

The other most commonly reported adverse event was gastrointestinal, including diarrhoea, nausea, dyspepsia and vomiting. Weight loss has also been observed.

All suspected adverse reactions to black triangle drugs such as lomitapide should be reported to the MHRA via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

3.4 Review of evidence

29 men and women with homozygous familial hypercholesterolaemia, aged 18 years or older, were recruited from 11 centres in four countries (USA, Canada, South Africa, and Italy). 23 of 29 enrolled patients completed both the efficacy phase (26 weeks) and the full study (78 weeks). The median dose of lomitapide was 40 mg a day. LDL cholesterol was reduced by 50% (95% CI −62 to −39) from baseline (mean 8·7 mmol/L [SD 2·9]) to week 26 (4·3 mmol/L [2·5]; p<0·0001). Levels of LDL cholesterol were lower than 2·6 mmol/L in eight patients at 26 weeks. Concentrations of LDL cholesterol remained reduced by 44% (95% CI −57 to −31; p<0·0001) at week 56 and 38% (—52 to −24; p<0·0001) at week 78. Gastrointestinal symptoms were the most common adverse event. Four patients had aminotransaminase levels of more than five times the upper limit of normal, which resolved after dose reduction or temporary interruption of lomitapide. No patient permanently discontinued treatment because of liver abnormalities

4. Summary of Key Points for Consideration

4.1 National guidance:

The NICE guideline CG71 “Identification and management of familial hypercholesterolaemia”;

The NICE TA94 “Statins for the prevention of cardiovascular events”. This guidance relates only to the initiation of statin therapy in adults with clinical evidence of cardiovascular disease (CVD) and in adults considered to be at risk of CVD. The guidance does not include specific advice for genetic dyslipidaemias (for example, familial hypercholesterolaemia).

Currently there is no date specified for a decision on Lomitapide.

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Scottish Medicines Consortium (SMC)

10th February 2014:

Lomitapide (Lojuxta®) is not recommended for use within NHS Scotland.

Indication under review: Adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g. nephrotic syndrome, hypothyroidism) must be excluded.

All Wales Medicines Strategy Group (AWMSG)
6th December 2013
In the absence of a submission from the holder of the marketing authorisation, lomitapide (Lojuxta®) cannot be endorsed for use within NHS Wales in adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH). Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolemia (e.g, nephrotic syndrome, hypothyroidism) must be excluded.

4.2 Efficacy

4.3 Potential Benefits over existing therapy

The benefit with lomitapide is its ability to consistently reduce LDL-cholesterol levels by approximately 40% in HoFH patients.

Comparative assessments against statins and other therapies for managing HoFH are not available and longer term safety data are lacking, so the appropriate place of lomitapide in therapy is uncertain.

4.4 Potential disadvantages

The reduction of LDL-C is a surrogate endpoint that is expected to correlate with a reduction in cardiovascular morbidity and mortality. The effect of lomitapide on cardiovascular outcomes will not be determined in the HoFH population given the rarity of this disease.

Substantial increases in liver fat content and transient elevations of liver enzymes have been reported. Patients with risk factors for liver toxicity were excluded from the PIII trial.

The most commonly reported adverse events were gastrointestinal, including diarrhoea, nausea, dyspepsia and vomiting.

4.5 Budgetary Impact

All strengths of lomitapide (5mg, 10mg, 20mg) are priced at £17,765 for 28 capsules. Annual cost of £230K per patient.

Homozygous familial hypercholesterolaemia is a rare condition, with an incidence of about one case per million people. Which would be 1 patient across Surrey. Although lomitapide is extremely high cost, treatment may reduce the requirement for LDL apheresis in some patients.

5. Conclusions and Recommendations

Lomitapide may be an option for prescribing by specialists for the treatment of patients with Homozygous Familial hypercholesterolaemia in adult patients who have not responded to conventional treatment lipid lowering treatments; noting that substantial increases in liver fat content and transient elevations of liver enzymes have been observed. Comparative assessments against statins and other therapies for managing HoFH are not available and longer term safety data are lacking, so the appropriate place of lomitapide in therapy is uncertain and national guidance from Scotland and Wales do not recommend its use.

CCGs need to decide if they wish to commission lomitapide for the financial year 2014/15. NHSE is expected to commission from April 2015.

PCN recommendation:
Black listed - Not routinely recommended for prescribing.

Appendix 1: Evidence search

Search terms used:

Resource	Used in this review?
National Library for Health (NHL) http://www.library.nhs.uk/Default.aspx A gateway site with access to other resources such as Reviews (Bandolier, Cochrane, CRD etc), Guidelines (e.g. NICE), Clinical Knowledge Summaries (CKS) and Journals including AMED, British Nursing Index, CINAHL, E-books, EMBASE, HMIC, MEDLINE, My Journals, PsycINFO, PubMed, Databases from Dialog.	✓
National Institute of Health and Clinical Excellence (NICE) http://www.nice.org.uk/ NICE produces national guidance in three areas of health: 1. Public health - guidance on the promotion of good health and the prevention of ill health 2. Health technologies - guidance on the use of new and existing medicines, treatments and procedures within the NHS 3. Clinical practice - guidance on the appropriate treatment and care of people with specific diseases and conditions within the NHS.	✓ (through NHL)
Bandolier http://www.medicine.ox.ac.uk/bandolier/index.html Bandolier is a website about the use of evidence in health, healthcare, and medicine. Information comes from systematic reviews, meta-analyses, randomised trials, and from high quality observational studies.	✓(through NHL)
Centre for Reviews and Dissemination http://www.york.ac.uk/inst/crd/ CRD undertakes high quality systematic reviews that evaluate the effects of health and social care interventions and the delivery and organisation of health care. Databases maintained by CRD include Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) Database	✓(through NHL)
Scottish Intercollegiate Guidelines Network (SIGN) http://www.sign.ac.uk/ Scottish equivalent of NICE	✓
Medical Services Advisory Committee (Australia) http://www.msac.gov.au/internet/msac/publishing.nsf/Content/home-1	✓

The principal role of the Medical Services Advisory Committee (MSAC) is to advise the Australian Minister for Health and Ageing on evidence relating to the safety, effectiveness and cost-effectiveness of new medical technologies and procedures.	
Canadian Agency for Drugs and Technologies in Health (CADTH) http://www.cadth.ca/index.php/en/home The Canadian Agency for Drugs and Technologies in Health (CADTH) is a national body that provides Canada's federal, provincial and territorial health care decision makers with credible, impartial advice and evidence-based information about the effectiveness and efficiency of drugs and other health technologies.	✓

Evidence retrieved

Guidelines

Reviews:

Journals

Brief description of any further published studies found outside those already covered in any reviews described above. E.g. if a review only covered a certain time period, the journals could be searched to find studies published outside these dates. Briefly describe in table below.

Appendix 2: Grading of evidence

- Ib: at least one randomised controlled trial

Appendix 3: References

1. Euopean Medicines Agency; Lojuxta Summary of Opinion; 13 May 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002578/WC500143787.pdf
2. Clinical Briefing Document – FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting; October 17, 2012.
3. Lojuxta Summary of Product Characteristics http://www.medicines.org.uk/emc/medicine/28321/SPC/Lojuxta+hard+capsules/
4. BNF April 2014
5. Drug Tariff.co.uk accessed 28/4/14
6. All Wales Medicines Strategy Group
7. Scottish Medicines Consortium http://www.scottishmedicines.org.uk
8. NICE guideline CG71 - Identification and management of familial hypercholesterolaemia; August 2008 http://publications.nice.org.uk/identification-and-management-of-familial-hypercholesterolaemia-cg71
9. NICE Cardiovascular disease - statins (TA94); January 2006 http://www.nice.org.uk/ta94
10. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study; Dr Marina Cuchel MD, Emma A Meagher MD, Prof Hendrik du Toit Theron MD, Dirk J Blom PhD, Prof A David Marais MD, Prof Robert A Hegele FRCP, Prof Maurizio R Averna MD, Prof Cesare R Sirtori MD, Prof Prediman K Shah MD, Daniel Gaudet MD, Claudia Stefanutti MD, Giovanni B Vigna MD, Anna ME Du Plessis MMed, Prof Kathleen J Propert ScD, William J Sasiela PhD, LeAnne T Bloedon MS, Prof Daniel J Rader MD, for the Phase 3 HoFH Lomitapide Study investigators; The Lancet, Volume 381, Issue 9860, Pages 40 - 46, 5 January 2013.

    http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)61731-0/abstract