NHS England

Clinical Commissioning Policy Proposition: Lomitapide for treating homozygous familial hypercholesterolaemia (adults)

Reference: NHS England 1679

Prepared by the National Institute for Health and Care Excellence (NICE) Commissioning Support Programme.

Published by NHS England, in electronic format only.

Contents

1 Executive Summary

Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Plain Language Summary

About homozygous familial hypercholesterolemia

Familial hypercholesterolemia (FH) is an inherited disease that results in very high levels of harmful cholesterol (a type of fat made by the body) from birth. In people with FH, there are raised levels of low-density lipoprotein cholesterol (LDL-C), also known as 'bad cholesterol'. FH is not caused by an unhealthy lifestyle, but is passed from generation to generation through one or more 'faulty genes' that are responsible for making and removing cholesterol in the body. People with the homozygous form of familial hypercholesterolemia (HoFH) have two faulty copies of these genes. It puts people at risk of heart diseases much earlier in their lifetimes than compared with the general population, causing heart attacks, heart valve disease (where the valves in the heart become damaged or diseased, which can affect blood flow and put additional pressure on the heart) and strokes.

See also, section 4 for additional definitions of terms used in this document.

About current treatments

There are several treatments available for people with HoFH. These include:

- Dietary and lifestyle advice. This may include advice on smoking cessation, diet, weight loss and physical activity. This is usually given in combination with one or more medical treatments for HoFH.
- Statins. These drugs block the enzyme (a type of chemical) in a person's liver that helps to make cholesterol. This leads to a reduction in your blood cholesterol level. This is usually the first cholesterol lowering drug given to people with HoFH.
- Additional cholesterol-lowering drugs given in combination with statins: such as ezetimibe, fibrates, bile acid sequestrants, and PCSK-9 inhibitors.
- Lipoprotein apheresis. This involves using a machine to filter the blood and remove cholesterol. This is only offered to patients with HoFH and LDL-C that remains persistently high despite the highest doses of medicines.
- Liver transplant, with or without a heart transplant. This may be considered if the disease progresses despite all the above described treatments. This procedure is performed very rarely for people with HoFH because of a lack of donor organs.

About the new treatment

Medicines for HoFH aim to reduce levels of cholesterol for people with HoFH. This is important because the often very high cholesterol levels caused by this condition can lead to premature death from heart disease, as early as in the third, second and even first decade of life. Established cholesterol lowering drugs (other than statins, see above) act mainly by improving the activity of low density lipoprotein receptors (LDLR, which take cholesterol from the blood). Lomitapide is thought to work in a different way to established cholesterol lowering drugs because it acts independently of the LDLR pathway. It is thought to block the action of a protein that releases LDL-C into the blood stream or absorbs LDL-C from the intestine. This decreases the amount of fat released into the blood and therefore reduces the level of cholesterol in the blood. Lomitapide is an add-on to existing cholesterol lowering treatments, with dietary and lifestyle advice, and with or without lipoprotein apheresis. It is therefore given if the disease progresses despite these treatments, and provides an additional treatment option before the consideration of liver transplant. If the addition of

lomitapide controls the disease, then patients and their clinicians may be able to consider stopping or reducing the frequency of apheresis.

What we have decided

NHS England has carefully reviewed the evidence to treat HoFH with lomitapide**.** We have concluded that there is enough evidence to consider making the treatment available.

2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission lomitapide.

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms.

For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether lomitapide will be routinely commissioned will be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

3 Proposed Intervention and Clinical Indication

Familial hypercholesterolemia (FH) is an inherited disease that results in exceptionally high levels of low density lipoprotein cholesterol (LDL-C) from birth. This causes rapid accumulation of LDL-C in the body, including in blood vessels, which leads to severe and progressive atherosclerosis (that is, thickening of the artery walls), and results in premature life-threatening major cardiac events such as heart attack, heart valve disease, stroke, the need for major cardiac surgery, and premature cardiac death. FH is caused by mutations in 1 or more genes responsible for cholesterol production and removal; people with homozygous hypercholesterolaemia (HoFH) have two defective copies of these genes. The term HoFH includes HoFH, autosomal recessive hypercholesterolaemia, compound heterozygous familial hypercholesterolaemia and double heterozygous familial hypercholesterolaemia. About 90% of cases are caused by mutations in LDLR. Clinical features of HoFH include small yellow bumps caused by collections of cholesterol under the skin or tendons (xanthomas), greyish-white rings of cholesterol around the iris (corneal arcus), and aortic and supra-aortic valve disease.

A diagram of the treatment pathway is presented in section 9.

The NICE guideline on the identification and management of familial hypercholesterolaemia states that healthcare professionals should consider a clinical diagnosis of HoFH in adults with LDL-C greater than 13 mmol/l. It states statins are usually given as initial treatment for all adults with FH, in addition to dietary and lifestyle advice (smoking cessation, dietary manipulation, weight loss, and increased physical activity). The NICE guidance does not contain any other recommendations for specific medicines that should be given in combination with a statin for people with HoFH; it instead states that prescribing of medicines for adults with HoFH should be undertaken within a specialist centre. Treatments that are used in clinical practice for people with HoFH include ezetimibe, a bile acid sequestrant (resin), a fibrate, and the PCSK-9 inhibitor evolocumab. The NICE guideline also states that lipoprotein apheresis should be considered for people with HoFH, with the timing for the initiation of this depending on factors such as the person's response to lipid-modifying drug therapy and presence of coronary heart disease. Finally, the NICE guideline states that liver transplantation should be considered as an option. Transplant is considered if disease progression occurs despite optimal treatment with lipid-lowering medication and lipoprotein apheresis. However, in clinical practice, it is a treatment of last resort, there is a shortage of organs, and the procedure is very rarely performed for people with HoFH because their need for a liver transplant is not prioritised above that of a patient with hepatic failure.

Lomitapide is thought to inhibit a protein in the body known as microsomal triglyceride transfer protein. This is involved in assembling fatty substances into larger particles, which are then released into the blood stream. The European public assessment report [EPAR] states that lomitapide represents a new class of drugs with a mechanism of action that differs from those of other classes of lipid-lowering medicines.

Lomitapide has a licence 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).

4 Definitions

Apoliprotein B (ApoB) – an important protein in the body for several types of lipoprotein (chylomicrons, very low density lipoprotein and low density lipoprotein). High levels of these are thought to be related to heart disease.

Atherogenic – causing increases in fatty deposits in the arteries.

Atherosclerosis – the thickening and hardening of artery walls, which can cause partial or total blockages in the arteries.

Cholesterol – a type of fat known as a lipid that is carried in the blood. It is produced by the liver and can also be found in some foods. It is essential for several processes in the body but too much causes atherosclerosis, increasing the risk of cardiovascular events.

Hepatic steatosis – an accumulation of fat in the liver (also known as 'fatty liver').

Homozygous familial hypercholesterolemia – familial hypercholesterolemia is an inherited disease that results in exceptionally high levels of low density lipoprotein cholesterol (LDL-C) from birth. The homozygous form of the disease is when there are 2 faulty copies of the genes responsible for cholesterol production and removal. The term HoFH includes HoFH, autosomal recessive hypercholesterolaemia (ARH), compound heterozygous familial hypercholesterolaemia and double heterozygous familial hypercholesterolaemia

High density lipoprotein (HDL) cholesterol – known as 'good' cholesterol because it absorbs cholesterol and transports it to the liver where it is removed from the body.

Lipoprotein – a protein in the body that carries cholesterol in the blood, to and from cells. They are particles made up of cholesterol and other lipids in the core surrounded by a single layer of phospholipid molecules. There are 4 main lipoproteins which can vary in size, content and density: chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL).

Lipoprotein apheresis – this involves using a machine to filter the blood and remove low density lipoprotein cholesterol (and other atherogenic lipoproteins).

Low density lipoprotein (LDL) cholesterol – known as 'bad' cholesterol because it has a tendency to deposit in the arteries. Over time this can cause a build-up of cholesterol, blood cells and other debris from the body. This causes plaque build-up which can thicken and block the artery, causing cardiovascular problems. LDL cholesterol makes up the majority of cholesterol in the body.

Microsomal triglyceride transfer protein – a protein that releases atherogenic lipoproteins into the blood stream or absorbs them from the intestine.

Non-HDL cholesterol – this is the sum of all 'bad' cholesterol, including LDL cholesterol. It is calculated by subtracting HDL cholesterol from total cholesterol.

Plaque – fatty deposits that form inside the artery wall consisting of cholesterol, fatty substances, cellular waste products, calcium and fibrin. Over time plaque build-up hardens and thickens the artery wall, causing it to narrow, and causes partial and sometimes total blockages. This blocks oxygen and blood getting to cells and leads to cardiovascular problems.

5 Aims and Objectives

This policy proposition considered: lomitapide as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without lipoprotein apheresis for treating adults with homozygous familial hypercholesterolaemia.

The objectives were to:

- Define the eligibility criteria for lomitapide
- Define the commissioning arrangements required for lomitapide.

6 Epidemiology and Needs Assessment

The estimated prevalence of HoFH is estimated to 1 per 1 million population in the UK (France et al, 2016), although this may be an underestimate because of phenotypic variation (France et al., 2016). Based on actual patient numbers being

treated in major apheresis centres, it is estimated that the prevalence of HoFH may be 1 in 670,000 adults in England.

Applying these prevalence rates to the England population aged 18 and over (approximately 44 million, ONS 2016), there are between 43 to 66 adult patients in England with HoFH. Based on prevalence rates and life expectancy, is it estimated there will be around 1 new case of HoFH every year.

It is not expected that all people with HoFH would start treatment with lomitapide, since some people will gain adequate control of their cholesterol levels using other treatments. In addition, it is a requirement in the licence for lomitapide that people must have a low fat diet (no more than 20% of their diet from fat) before and during treatment, and some people may have difficulty adhering to this.

Assuming the higher prevalence estimate (66 adults in England), it is estimated that 34 people would be eligible for treatment with lomitapide in NHS practice in England, based on the following assumptions for people with HoFH that is not controlled with existing treatments including lipoprotein apheresis:

- Approximately 22% (14 patients) of people with HoFH have disease that is LDLR negative (based on combining published data from registries in Spain, Sánchez-Hernández, 2016 and Alonso, 2016). LDLR negative disease does not respond to PCSK-9 inhibitors (France et al. 2016), therefore these patients would be eligible for lomitapide.
- The remaining 78% (51 patients) would try a PCSK-9 inhibitor:
    - Approximately 30% of people would have disease that does not respond to treatment (Raal et al. 2017) (n=15) and therefore would be eligible for lomitapide.
        - Of the 70% of people who do respond to a PCSK-9 inhibitor, approximately 50% would have disease that initially responds but does not reach the recommended LDL-C target (estimated by the company who market lomitapide) (n=18) and therefore be eligible for lomitapide.
- The total number of people eligible for lomitapide would be 47. But of these

28% (based on the LOWER registry), would be unwilling or unable to commit to the low-fat diet required to take lomitapide, avoid alcohol, or because of co-morbidities resulting in liver toxicity concerns.

- Therefore it is estimated that 34 patients (72% of those eligible for lomitapide) will remain on it. It is estimated this figure will remain reasonably steady year on year, with any new cases offset by people stopping treatment because of lack of effectiveness, adverse events or death.

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication.

Summary of evidence

NHS England considered evidence from 8 studies on the clinical effectiveness and safety of lomitapide. Lomitapide was given in addition to other lipid-lowering therapy.

The main evidence considered on the effectiveness of lomitapide is from Cuchel et al. 2013 (n= 29). A long-term, uncontrolled, follow on study of Cuchel et al. 2013 reported by Blom et al. 2017 was also considered. Another smaller (n=9) phase 3, single arm, open label study was reviewed (Harada Shiba et al. 2017, conducted only in a Japanese population). Other studies included 2 single arm, open label studies (Cuchel et al. 2007, a phase 2 dose escalation [proof of concept] study which included 6 patients, and Yahya et al. 2016, which included 4 patients), and 3 uncontrolled retrospective studies with sample sizes ranging from 4 to 15 patients (D'Erasmo et al. 2017, Roeters van Lennep et al. 2015 and Stefanutti et al. 2016).

In Cuchel et al. 2013, current lipid-lowering therapy was maintained from 6 weeks before baseline through to at least week 26, where 27 patients were being treated with statins, 22 with ezetimibe in combination with a statin, 3 with niacin, 1 with a fibrate and 1 with a bile acid sequestrant. Eighteen subjects were regularly undergoing apheresis with a frequency that ranged from weekly to every 6 weeks.

The key outcome reported in all studies was change in low density lipoprotein cholesterol (LDL-C) from baseline to follow up. The European Public Assessment Report (EPAR) for lomitapide states that although the long-term effect of lipid

reduction of lomitapide on cardiovascular events was not investigated, reduction in LDL-C is considered an important surrogate endpoint with potential benefits in terms of cardiovascular outcomes. Studies assessing long-term cardiovascular outcomes and survival suggests that maximum lipid-lowering treatment (including lipoprotein apheresis) ensures long-term reduction in the cholesterol burden and risk of cardiovascular complications and improves survival:

- Thompson et al. 2017 (n=133) did a retrospective survey of lipid levels and clinical outcomes for people with HoFH treated with a combination of lipid lowering treatments between 1990 and 2014 in South Africa and the UK. It found that the risk of death of people with the highest levels of serum cholesterol (>15.1 mmol/L) (which is 90% LDL-C in people with HoFH), was 11.5 times higher than those with the lowest levels of serum cholesterol (<8.1mmol/L). And the risk of death for those with cholesterol levels 8.1 to 15.1mmol/L was 3.6 times higher than those with the lowest levels (<8.1mmol/L). Both of these results were statistically significant (p<0.001). The study also found statistically significant results for cardiovascular specific death and major adverse cardiac events.
- In a retrospective single-centre study, Bruckert et al. 2017 evaluated the association of cardiovascular complications with changes in cholesterol over time (up to 38 years) in 53 people with HoFH, as well as total cholesterol burden. It found that cumulative total cholesterol was highly associated with the incidence of an adverse clinical event. A 100 mmol/L increase in cumulative total cholesterol (an average exposure of 10 mmol/L per 10 years or 20 mmol/L per 5 years) was associated with a doubling of the risk of a cardiovascular event.

Clinical effectiveness

Cuchel et al. 2013 (n=29) found by week 26 and week 78 that there were statistically significant reductions of 50% (from 8.7 to 4.3mmol/L) and 38% respectively (p<0.0001 for both outcomes) in LDL-C when lomitapide at maximum tolerated dose was added to other lipid-lowering treatments. Blom et al. 2017 (the extension study of Cuchel et al. 2013) found the reduction in LDL C levels at week 126 was −45.5% (p<0.0001). This finding was supported by 2 additional studies,

which found statistically significant reductions of 42% at week 26 ($p<0.0001$, Harada-Shiba et al 2017, n=9) and 68.2% over a treatment duration of 8 to 86 months ($p<0.05$, D'Erasmo et al, 2017, n=15). Furthermore, from baseline to week 246, Blom et al. 2017 reported that a total of 14 patients taking lomitapide had LDL-C levels less than ~2.5 mmol/L and 11 patients had LDL-C levels less than ~1.8 mmol/L on at least 1 occasion (no statistical analyses reported).

Secondary outcomes used to assess the efficacy of lomitapide included the change in levels of non-high density lipoprotein cholesterol (non HDL-C which is the sum of all 'bad' cholesterol, including LDL cholesterol) and apolipoprotein B (high levels are thought to be related to heart disease) from baseline to follow up. Cuchel 2013 demonstrated statistically significant reductions of approximately 50% ($p<0.0001$) for both outcomes, and this was supported by several other studies.

Although not reported as an outcome measure in the majority of studies, the addition of lomitapide to existing lipid-lowering treatments resulted in a decreased frequency of lipoprotein apheresis or stopping lipoprotein apheresis in some patients with HoFH (Cuchel et al. 2013, D'Erasmo et al. 2017, Harada Shiba et al. 2017, Roeters van Lennep et al. 2015, Stefanutti et al. 2016). This may benefit patients because lipoprotein apheresis is needed about once every 2 weeks (France et al., 2016) and can be invasive, time consuming, and impact quality of life of patients (Bruckert, 2014).

Results from a South African modelling study (Leipold et al. 2017) which took hazard ratios from a treated HoFH population model suggested that if a person with HoFH was prescribed lomitapide in addition to standard of care from 18 years of age, the median increase in life expectancy compared with not taking lomitapide was 11.2 years, with a median 5.6-year delay in time to first cardiovascular event. These data are based on an estimate of a 38% lowering in LDL C levels with lomitapide. NICE has not validated any methods used to generate these estimates and the estimates are not actual data, therefore results from this modelling study need to be interpreted with caution.

Safety

There were no treatment related deaths reported in the included studies. Adverse

events described as the "most serious" in the SPC for lomitapide were liver aminotransferase abnormalities (and the frequency of increases in these levels were reported as “very common” in the SPC). Raised aminotransferase levels in the blood suggest that the liver may not be functioning as it should do because of an adverse effect on it, and is associated with liver disease. Elevations in serum aminotransferases (AST, ALT or both) of 3 or 5 times the upper level of normal (ULN) were reported in the majority of studies. These occurred in 34.5% (n=10), 21.1% (n=4) and 33.3% (n=3) of patients in Cuchel et al. 2013, Blom et al. 2017 and Harada Shiba et al. 2017 respectively. Treatment discontinuation because of elevated serum aminotransferases was reported in 2 studies (n=1 in each study, Harada Shiba et al. 2017 and Roeters van Lennep et al. 2015). Results from the studies suggest that these elevations are temporary and can be reversible with both reductions in dose and short term withdrawal of lomitapide.

Studies for lomitapide suggest that there is an increased risk of hepatic fat accumulation whilst on treatment with lomitapide (some fat in the liver is normal, but when there is too much this can lead to health problems, including cirrhosis and liver failure). The SPC notes that the frequency of hepatic steatosis is reported as “common”.

The EPAR states that association of lomitapide treatment with liver fat accumulation was observed, however data are limited. It also states that the adverse effect of lomitapide on the liver is related to the pharmacodynamic effect of lomitapide and the potential long-term development of hepatotoxic effects, such as fibrosis, cannot currently be assessed, due to limited data.

The most commonly reported adverse events during lomitapide treatment were gastrointestinal-related. Cuchel et al. 2013 reported that 93.1% (n=27) of patients experienced gastrointestinal related adverse events (commonly diarrhoea, nausea, dyspepsia and vomiting) during the study. Most were reported to be mild or moderate, although 3 patients permanently discontinued treatment with lomitapide because of gastrointestinal related adverse events. Gastrointestinal events were frequently reported in several other studies. The EPAR states “severe gastrointestinal adverse events that occur mostly at the start of treatment, are considered manageable for most patients by temporary treatment discontinuation or

temporary down titration of the dose".

Strengths

Outcome data for assessing the safety and effectiveness of lomitapide were available from several studies. The best available evidence for this review is based on a phase 3 single arm open label study (Cuchel et al. 2013, n=29) that was also reported in the EPAR. This demonstrated statistically significant improvements in key outcomes such as reduction in LDLC, reduction in non-HDLC, adverse events and hepatic fat, and the findings were supported by several smaller studies.

Limitations

The results for these outcomes may need to be interpreted with caution because of the following reasons:

- Results for the safety and tolerability of lomitapide are based on studies that included a small number of patients (between 4 to 29 patients).
- Although long-term follow-up data up to 246 weeks are available for 1 study (in Blom et al 2017, the long-term extension of Cuchel et al 2013), most studies and primary outcomes were recorded over a short-term period. Therefore more data are needed to confirm the long-term safety and effectiveness of lomitapide. Long-term safety and efficacy of lomitapide in patients with HoFH is being studied in the Lomitapide Observational Worldwide Evaluation Registry (LOWER) study (NCT02135705), a long-term (target follow up of 10 years) study of patients taking lomitapide, to provide further data on its safety and effectiveness, including its side effects on the liver, stomach, gut, and cardiovascular system (to assess the progression of atherosclerosis).
- Studies were open label, non-randomised and uncontrolled which has the potential to introduce bias.
- Studies did not adjust for confounding factors (including demographic factors, duration of the disease, comorbidity, co-medication and dietary composition) which may have influenced the results.
- People with HoFH have a high risk of cardiovascular disease. The included studies did not report any cardiovascular events as an outcome (although the

EPAR for lomitapide states that reduction in LDL-C is considered an important surrogate endpoint with potential benefits in terms of cardiovascular outcome, and studies support this (Bruckert et al. 2017 and Thompson et al. 2017)).

8 Proposed Criteria for Commissioning

It is proposed to routinely commission lomitapide when the following criteria are met:

- Lomitapide should only be considered when HoFH is not adequately controlled by existing treatments and people are at high risk of cardiovascular events:
    - Existing treatments: These should include ALL of the treatments most commonly used from baseline to week 26 in the main trial, as long as they are clinically indicated: statins, ezetimibe in combination with a statin, and apheresis. In addition, evolocumab if HoFH is LDLR defective or unknown.
    - HoFH that is not adequately controlled and at high risk of cardiovascular events: where LDL-C is as follows (based on specific therapeutic targets for LDL-C lowering in HoFH set by HEART UK (France et al. 2016) and the European Atherosclerosis Society)
        - >2.5mmol/L for adults with FH
        - >1.8mmol/L for adults with atherosclerotic cardiovascular disease.

AND

- Confirmation of HoFH should be obtained using 1 of the following criteria:
    - Documented functional mutation(s) in both LDL receptor alleles or alleles known to affect LDL receptor functionality, OR;
    - Untreated LDL-C greater than 13 mmol/L

AND

- Patients should have a low fat diet prior to, and during, treatment with lomitapide (<20% energy from fat)

A multidisciplinary team (MDT) made up of people including a lipidologst, specialist nurse and dietician should be responsible for prescribing lomitapide, monitoring and

follow up of patients.

Stopping criteria

- Discontinue treatment with lomitapide if:
    - lomitapide does not control disease (stop lomitapide treatment if LDL-C levels do not drop by 20% of pre-lomitapide levels)
    - the patient is unwilling or unable to adhere to a low fat diet (<20% of energy from fat). This should be monitored throughout treatment.
- Modify or discontinue treatment with lomitapide where liver damage may be occurring as guided by the SPC.

Please see the SPC for full prescribing details. The EPAR states that association of lomitapide treatment with liver fat accumulation was observed, however data are limited. To minimise the risk of progressive liver disease, the SPC for lomitapide requires that patients have their liver function tests monitored regularly. It also includes several special warnings and precautions for use related to liver abnormalities and liver monitoring, monitoring of liver function tests, dose modification based on elevated hepatic aminotransferases, hepatic steatosis and risk of progressive liver disease, monitoring for evidence of progressive liver disease, concomitant use of statins and reduced absorption of fat soluble vitamins and serum fatty acids.

9 Proposed Patient Pathway

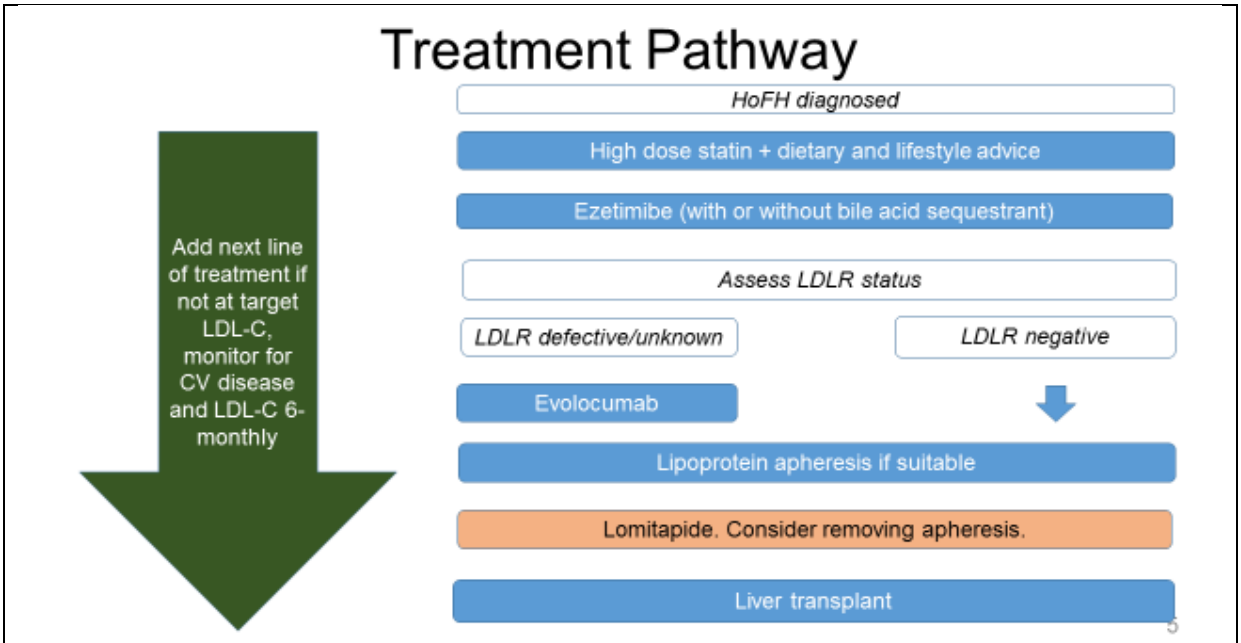
Treatments for HoFH are designed to lower cholesterol. This is because high cholesterol levels have a very strong association with increased risk of death and adverse cardiovascular outcomes, so patients will get significant benefits if this can be achieved. Specific therapeutic targets for LDL-C lowering in HoFH are set by HEART UK and the European Atherosclerosis Society (EAS) at LDL-C of less than 2.5 mmol/L 100 mg/dL) for adults, or less than 1.8 mmol/L (70 mg/dL) in adults with clinical atherosclerotic cardiovascular disease. There is therefore generally a stepped approach to the treatment pathway – if patients have HoFH with LDL-C above these levels, this carries an increased risk of adverse cardiovascular events, and patients and their clinicians would consider adding the next treatment to reduce

levels of LDL-C.

The NICE guideline on the identification and management of familial hypercholesterolaemia, recommends statins as the initial treatment for all adults with familial hypercholesterolaemia (FH) in addition to dietary and lifestyle advice. The NICE guidance does not contain any other recommendations for specific medicines that should be given in combination with a statin for people with HoFH; it instead states that prescribing of medicines for adults with HoFH should be undertaken within a specialist centre. In clinical practice, ezetimibe with or without a bile acid sequestrant would first be added to a statin. The PCSK-9 inhibitor, evolocumab, would then be offered. However, France et al. 2016 states that evolocumab would only be given to patients who have HoFH that is either LDLR defective or unknown, because receptor negative patients do not respond to PSCK9 inhibitors (although if testing was not possible, this treatment may be tried first). Lipoprotein apheresis would then be offered, depending on the response to treatment and presence of coronary heart disease. If disease progression occurs despite treatment with lipid-lowering medication and lipoprotein apheresis, liver transplantation would be considered, although this is rare because of a lack of donor organs. Lomitapide would provide an additional treatment option before liver transplantation. If effective for an individual patient, it may also allow a reduction in lipoprotein apheresis.

Lomitapide should be prescribed at specialist centres (see section 10).

Figure 1: Treatment pathway for people with HoFH



Acronyms

HoFH: Homozygous familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; LDLR – low density lipoprotein receptor.

10 Proposed Governance Arrangements

Currently 6 centres provide lipoprotein apheresis in England. These centres should be responsible for prescribing lomitapide, monitoring and follow up of patients. Lomitapide is provided via home delivery.

Any provider organisation treating patients with this intervention is required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust's Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Provider organisations must register all patients using prior approval system software and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

11 Proposed Mechanism for Funding

The funding and commissioning will be managed through the relevant local NHS England Specialised Commissioning Team

12 Proposed Audit Requirements

Long-term safety and efficacy of lomitapide in patients with HoFH is being studied in the Lomitapide Observational Worldwide Evaluation Registry (LOWER) study (NCT02135705). This a long-term study in patients taking lomitapide to provide further data on its safety and effectiveness, including its side effects on the liver, stomach, gut, and cardiovascular system (to assess the progression of atherosclerosis). The study will also provide data on pregnancies in women taking the medicine, and on healthcare professionals' compliance with the recommendations to screen and monitor patients before and during treatment. All patients eligible for lomitapide must be registered on LOWER.

13 Documents That Have Informed This Policy Proposition

The documents that have informed this policy proposition include a review of the clinical evidence available for lomitapide and a submission from Amryt Pharma. Additional evidence sources are listed in the table of references below.

14 Date of Review

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

15 References

Alonso R, et al. 2016. Clinical and molecular characteristics of homozygous familial hypercholesterolemia patients: Insights from SAFEHEART registry. Journal of Clinical Lipidology. 10(4):953-61

Blom D J, Averna M R, Meagher E A, et al. (2017) Long-Term Efficacy and Safety of the Microsomal Triglyceride Transfer Protein Inhibitor Lomitapide in Patients With Homozygous Familial Hypercholesterolaemia. Circulation 136, 332-335

Bruckert E, Kalmykova O, Bittar R et al. (2017) Long-term outcome in 53 patients with homozygous familial hypercholesterolaemia in a single centre in France. Atherosclerosis 257, 130-137

Cuchel, M., Bruckert, E., Ginsberg, H. et al. (2014). Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. European Heart Journal, 35(32), 2146-2157

Cuchel M, Blom DJ, Averna MR et al (2013) Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet 381, 40-6

Cuchel M, Bloedon LT, Szapary PO et al. (2007) Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolaemia. New England Journal of Medicine 356, 148-56

D'Erasmo L, Cefalu A B, Noto D, et al. (2017) Efficacy of Lomitapide in the Treatment of Familial Homozygous Hypercholesterolaemia: Results of a Real-World Clinical Experience in Italy. Advances in Therapy 34, 1200-1210

France M, Rees A, Datta D et al. (2016) HEART UK statement on the management of homozygous familial hypercholesterolaemia in the United Kingdom. Atherosclerosis, 255 128-139

Ito M and Watts G (2015) Challenges in the Diagnosis and Treatment of Homozygous Familial Hypercholesterolemia. Drugs. 75 (15) 1715-1724

Harada-Shiba M et al. (2017) Efficacy and Safety of Lomitapide in Japanese Patients with Homozygous Familial Hypercholesterolaemia. Journal of Atherosclerosis & Thrombosis 24, 402-411

Leipold R, Raal F, Ishak J, Hovingh K, Phillips H (2017) The effect of lomitapide on cardiovascular outcome measures in homozygous familial hypercholesterolemia; a modelling analysis. European Journal of Preventative Cardiology.

Raal R et al (2017) Long-term treatment with evolocumab added to conventional drug therapy, with or without apheresis, in patients with homozygous familial hypercholesterolaemia: an interim subset analysis of the open-label TAUSSIG study. Lancet Diabetes and Endocrinology. 5(4):280-290

Roeters van Lennep RJ, Averna M, and Alonso R (2015) Treating homozygous familial hypercholesterolaemia in a real-world setting: Experiences with lomitapide. Journal of Clinical Lipidology 9, 607-17

Sánchez-Hernández RM, et al. 2016. Homozygous Familial Hypercholesterolemia in Spain: Prevalence and Phenotype-Genotype Relationship. Circulation: Cardiovascular Genetics. 9(6):504-510

Stefanutti C, Morozzi C, Di Giacomo, et al. (2016) Management of homozygous familial hypercholesterolaemia in real-world clinical practice: A report of 7 Italian patients treated in Rome with lomitapide and lipoprotein apheresis. Journal of Clinical Lipidology 10, 782-9

Thompson GR., Dirk J et al. (2017) Survival in homozygous familial hypercholesterolaemia is determined by the on-treatment level of serum cholesterol, European Heart Journal, ehx317

Yahya R, Favari E, Calabresi L, Verhoeven A J et al. (2016) Lomitapide affects HDL composition and function. Atherosclerosis 251, 15-18

END