New Medicine Recommendation
Colesevelam (Cholestagel®)
Combination and monotherapy for familial hypercholesterolaemia

Recommendation:

Black - NOT recommended for use by the NHS in Lancashire.

- Colesevelam (Cholestagel®) is NOT recommended as combination or monotherapy for familial hypercholesterolaemia. Clinical evidence indicates that the drug is poorly tolerated and the trials were weak in significant areas such as the inclusion of small numbers of patients, only demonstrating surrogate endpoints or being conducted using nonstandard co-administered drugs. There are similar, established drugs for the treatment of the condition for which there were no head to head trials with Colesevalam therefore relative clinical efficacy cannot be directly demonstrated.

Summary of supporting evidence:

- Primary dyslipidaemias, including familial hypercholesterolaemia (FH), are lipid disorders that are genetic in origin. FH is the most common inherited lipid metabolism disorder in its heterozygous form. In the UK heterozygous FH affects 1 in 500 of the UK population. [1]
- Statin therapy is the first-line treatment for patients with the vast majority of dyslipidaemias. NICE CG 71 recommends the prescribing of a high-intensity statin at the maximum licensed dose or at the maximum tolerated dose to achieve a reduction in LDL cholesterol concentration of greater than 50% from baseline. [2]
- Colesevelam is a lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. [3] Colesevelam is a third-line agent, behind statins and ezetimibe. [2]
- The main body of evidence for the use of colesevelam in familial hypercholesterolaemia comes from the European Public Assessment Reports (EPAR).
- **Study GTC-48-301** was a randomised, double-blind, parallel design, placebo-controlled pivotal phase III dose-response study. The study was conducted to determine the long-term efficacy and safety of colesevelam. [4]
- Reductions in LDL cholesterol ≥9% were obtained with colesevelam doses of 2.3gram and ≥15% at doses of 3.8gram and 4.5gram daily. However, only a limited number of the patients reached the clinically more relevant target of LDL cholesterol <3mmol/L. More than 50% of

patients achieved at least a 15% reduction in LDL cholesterol regardless of baseline figures. 6% and 14% of patients were non-responders in the colesevelam 3.8gram and 4.5gram group respectively. Small but significant increases in HDL cholesterol were also noted. [4]

- **Study GTC-48-302** was a randomised, double-blind, parallel design, placebo-controlled pivotal phase III dose regimen study. The intention of the study was to assess safety and efficacy of once daily dosing of colesevelam. [4]
- Percentage change in LDL cholesterol was similar in the evaluable population with LDL reductions of 20%, 16% and 19% for morning, evening and twice daily treatment groups respectively. Triglycerides increased more in the morning dosing group than the evening dosing group. [4]
- **A variation assessment report** was published by the EMA in 2010 following a submission by the manufacturer to extend the license of Cholestagel. [5] The variation report considered two new studies: **CHOL00107** and **WEL408**. [5]
- **CHOL00107** was a phase IV randomised, double-blind, placebo-controlled, parallel-group, multicentre study of colesevelam as add-on therapy in patients with familial hypercholesterolaemia.
- Colesevelam, as add-on therapy to a maximally-tolerated and stable regimen of statin of ezetimibe, significantly reduced LDL cholesterol levels compared to placebo at week six as well as week 12 of treatment (week-12 assessment formed a secondary endpoint). Mean LDL cholesterol levels were 3.9mmol/L (standard deviation = 0.98) and 3.8mmol/L (0.98) at baseline in the colesevelam treatment and placebo groups respectively. At week six, defined by the primary endpoint, mean LDL cholesterol levels were 3.3mmol/L (0.78) in the colesevelam group and 4.0mmol/L (1.10) in the placebo group, a percentage change of -11.3% and +7.0% respectively. The difference in percentage change was -18.7% ($p < 0.0001$) in favour of colesevelam active treatment.
- **WEL408** was a multi-centre, randomised, double-blind, placebo-controlled, parallel group study. The objectives of the study were: a) to compare the effect of colesevelam in combination with ezetimibe to ezetimibe alone on LDL cholesterol concentration in patients with primary hypercholesterolaemia and b) to compare the effects of colesevelam in combination with ezetimibe and simvastatin to ezetimibe in combination with simvastatin. [5]
- Colesevelam plus ezetimibe and colesevelam placebo plus ezetimibe both resulted in significant mean decreases in LDL cholesterol levels compared with baseline (least squares % change from baseline [standard error] -32.3 [1.8] and -21.4 [1.8] respectively [both $p < 0.0001$]). Colesevelam in addition to ezetimibe resulted in an additional 11% reduction in LDL cholesterol levels from baseline to ezetimibe treatment and placebo. [6] [5]
- **Rosenson, 2006**, published a double-blind, placebo-controlled, randomised trial. [7] The study

focused on the reduction of LDL particle number and size in hypercholesterolaemia after treatment with colesevelam.

- LDL cholesterol concentrations were lower in the two groups that received the highest doses of colesevelam (3.0gram and 3.75gram daily) after six weeks (-9.5% [p = 0.0007] and -11.3% [p = 0.0001] respectively). Mean LDL particle size increased only at the highest dose of colesevelam (3.75gram daily; 1.1% increase in size [p = 0.01]). The authors stated that particle size was a weak predictor of cardiovascular risk. Mean LDL particle number was reduced by 6.8% (p = 0.03) in the 3.0gram daily and 13.7% (p = 0.0002) in the 3.75gram colesevelam treatment groups.
- **Davidson et al, 2010**, published a 50-week extension study on the safety and efficacy of colesevelam in adults with primary hypercholesterolaemia. [8] The study was an open-label, multicentre, titration-based extension study.
- At week 50, LDL cholesterol levels were significantly reduced from baseline across all treatment regimens (-29.6mg/dL [185.8 – 156.2mg/dL; 15.0% reduction]; p < 0.001). The mean change from baseline of LDL cholesterol for those participants who received colesevelam monotherapy: all dosage regimens and maximum dosage regimen were lower: -10.9% (p < 0.001) and -12.9% (p < 0.001) respectively. The cohort of patients that received both colesevelam and statin therapy realised the greatest reduction in LDL cholesterol levels, mean change from baseline was -34.2% (p < 0.001). [8]
- The potential budget impact to the Lancashire health economy would be £338,865 - £593,340 per year. Although, based on the applicant's estimate, **the cost of treating 30 patients at the maximum dose for one year would be £40,929.**

Details of Review

Name of medicine (generic & brand name)**:** Colesevelam (Cholestagel®)
Strength(s) and form(s): 625mg film-coated tablets
Dose and administration: Combination therapy (in combination with a statin, with or without ezetimibe): four to six tablets per day. Monotherapy: three tablets twice a day up to a maximum of seven tablets per day. [3]
BNF therapeutic class / mode of action: 2.12 Lipid-lowering drugs. Bile acid sequestrant. [9]
Licensed indication(s): [3] Colesevelam co-administered with a 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin) is indicated as adjunctive therapy to diet to provide an additive reduction in low-density lipoprotein cholesterol (LDL-C) levels in adult patients with primary hypercholesterolaemia who are not adequately controlled with a statin alone. Colesevelam as monotherapy is indicated as adjunctive therapy to diet for reduction of elevated total-cholesterol and LDL-C in adult patients with primary hypercholesterolaemia, in whom a statin is considered inappropriate or is not well-tolerated. Colesevelam can also be used in combination with ezetimibe, with or without a statin, in adult patients with primary hypercholesterolaemia, including patients with familial hypercholesterolaemia.
Proposed use (if different from, or in addition to, licensed indication above): In combination with ezetimibe, with or without a statin, in adult patients with primary hypercholesterolaemia, including patients with familial hypercholesterolaemia.
Course and cost: [9] Colesevelam 2.5gram – 4.375gram daily 180 x 625mg tablets = £96.10 Potential cost per annum per patient = £779.48 - £1364.31
Current standard of care/comparator therapies: [9] Cholestyramine 4gram – 36gram daily 50 x 4gram sachets= £31.85 Potential cost per annum per patient = £232.51 - £2092.54 Colestipol hydrochloride 5gram – 30gram daily 30 x 5gram sachets = £15.05 Potential cost per annum per patient = £183.11 - £1098.64
Relevant NICE guidance: There are no NICE technology appraisals that are relevant to the use of colesevelam. The SMC and AWMSG did not endorsed the use of colesevelam in combination with ezetimibe, with or without a statin, for the treatment of adult patients with primary hypercholesterolaemia, including patients with familial hypercholesterolaemia in Scotland and Wales respectively. The manufacturer did not make a submission for review to either the SMC or AWMSG for the above indication. NICE Clinical Guideline 71: Familial hypercholesterolaemia: identification and management. [2] 1.3.1.2

Statins should be the initial treatment for all adults with FH.

1.3.1.3

Healthcare professionals should consider prescribing a high-intensity statin to achieve a recommended reduction in LDL-C concentration of greater than 50% from baseline (that is, LDL-C concentration before treatment).

1.3.1.6 – 1.3.1.8

Ezetimibe monotherapy is recommended as an option for the treatment of adults with heterozygous-FH who have contraindications to or are intolerant to statin therapy.

Ezetimibe, co-administered with initial statin therapy, is recommended as an option for the treatment of adults with heterozygous-FH who have been initiated on statin therapy when:

- Serum total or LDL-C concentration is not appropriately controlled on maximal statin therapy or dose titration is limited by tolerability, and
- Consideration is being given to changing from initial statin therapy to an alternative statin.

1.3.1.15

Adults with FH with intolerance or contraindications to statins or ezetimibe should be offered a referral to a specialist with expertise in FH for consideration for treatment with either a bile acid sequestrant (resin), nicotinic acid, or a fibrate to reduce their LDL-C concentration.

1.3.1.16

The decision to offer treatment with a bile acid sequestrant (resin), nicotinic acid or a fibrate in addition to initial statin therapy should be taken by a specialist with expertise in FH.

1.3.1.29

Healthcare professionals should consider offering fat-soluble vitamin (vitamins A, D and K) and folic acid supplementation for adults or children/young people with FH who are receiving long-term treatment with bile acid sequestrants (resins).

Background and context

Cholesterol plays an essential role in many biological functions, including storing energy. The term dyslipidaemia represents a spectrum of lipid disorders, of which, familial hypercholesterolaemia is just one. The ultimate aim of treatment is to reduce the risk of cardiovascular events occurring. [1]

Primary dyslipidaemias, including familial hypercholesterolaemia (FH), are lipid disorders that are genetic in origin. FH is the most common inherited lipid metabolism disorder in its heterozygous form. In the UK heterozygous FH affects 1 in 500 of the UK population. [1]

Patients with FH have excess circulating LDL (low-density lipoprotein) cholesterol and total cholesterol from birth and have a substantially higher risk of cardiovascular disease. FH is suspected in individuals who present with a total cholesterol of >7.5mmol/L, particularly if there is evidence of premature cardiovascular disease in the patient's family. Patients with FH may also exhibit signs of cholesterol deposition including corneal arcus, tendon xanthoma and xanthelasma. Early identification and treatment of patients with FH is vital. [1] [10]

Homozygous FH is much more severe than the heterozygous form and could result in cardiovascular events occurring in patients as young as two. The prevalence of homozygous FH is much less than that of heterozygous, affecting around 1 in 1,000,000 worldwide. [1] [10]

Dyslipidaemias are mainly asymptomatic. That is until the patient presents with their first significant cardiovascular event. Therefore, many people in the UK may not be identified early enough to commence primary prevention. It is estimated that only 15% of those with FH are identified within the population. [10]

The National Institute for Health and Clinical Excellence (NICE) published a clinical guideline in 2008 (NICE CG 71) regarding the identification and management of familial hypercholesterolaemia. [2]

Statin therapy is the first-line treatment for patients with the vast majority of dyslipidaemias. NICE CG 71 recommends the prescribing of a high-intensity statin at the maximum licensed dose or at the maximum tolerated dose to achieve a reduction in LDL cholesterol concentration of greater than 50% from baseline. Because of the very high levels of LDL cholesterol that can be present in FH statins alone may not be sufficient to reduce LDL and total cholesterol levels to within an accepted level. [10] [2]

Bile acid binders act by binding to bile acids in the intestines and preventing reabsorption. This action stimulates the conversion of cholesterol to bile acids and encourages the removal of circulating LDL cholesterol. Bile acid binding agents reduce total cholesterol and LDL cholesterol but can increase triglyceride levels. [10] [3]

Cholestyramine and cholestipol are both bile acid binders that have shown a trend towards reduced mortality and non-fatal myocardial infarction (MI) in one trial. However, their use is

limited in clinical practice by poor tolerability, drug interactions and increasing circulating triglycerides. [10]

Pharmacology and pharmacokinetics

Colesevelam is a lipid-lowering polymer that binds bile acids in the intestine, impeding their reabsorption. As the bile acid pool becomes depleted, the hepatic enzyme, cholesterol 7-alpha-hydroxylase, is upregulated which increases the conversion of cholesterol to bile acids. This causes an increased demand for cholesterol in the liver cells, resulting in the dual effects of increasing transcription and activity of the cholesterol biosynthetic enzyme, hydroxymethyl-glutaryl-coenzyme A (HMG-CoA) reductase, and increasing the number of hepatic low-density lipoprotein receptors. A concomitant increase in very low density lipoprotein synthesis can occur. These compensatory effects result in increased clearance of LDL cholesterol from the blood, resulting in decreased serum LDL cholesterol levels. [3]

Colesevelam is not absorbed from the gastrointestinal tract. [3]

Summary of evidence

Summary of efficacy data in proposed use:

The main body of evidence for the use of colesevelam in familial hypercholesterolaemia comes from the European Public Assessment Reports (EPAR). There also two randomised controlled trials in the literature.

Regulatory information

Nine phase II and III studies were reviewed by the European Medicines Agency (EMA) as part of the licensing submission for colesevelam. Seven of those studies reviewed were randomised controlled trials (RCTs) and two were open-label, non-controlled studies. The RCT data consisted of five phase II studies and two pivotal phase III studies. I will consider data from the two pivotal studies in depth and I will summarise data from the five phase II studies.

In all studies, patients were placed on a controlled diet low in fat and dietary cholesterol for at least two weeks prior to study initiation and all patients were required to adhere to a low-fat, low cholesterol diet while being enrolled in the studies. [4]

No formal power calculations were completed for any of the studies. Intention to treat (ITT) populations were defined as those patients who were randomised, took at least one dose of study medication and had at least one post-baseline fasting lipid evaluation. The evaluable population was defined as those patients who completed the study and were at least 80% overall compliant to study medication. [4]

Study GTC-48-301 was a randomised, double-blind, parallel design, placebo-controlled pivotal phase III dose-response study. The study was conducted to determine the long-term efficacy and safety of colesevelam. 494 participants with a previous diagnosis of primary hypercholesterolaemia were included. 400 entered the study and received colesevelam and 94

received placebo. Participants in the active treatment arm received between 2.3gram and 4.5gram of colesevelam daily in divided doses. The primary efficacy endpoint was the change in serum LDL-C from baseline to completion of treatment. The study lasted six months. [4]

382 (77%) completed the study and 467 were considered part of the ITT populations. 353 were part of the evaluable population. Reductions in LDL cholesterol ≥9% were obtained with colesevelam doses of 2.3gram and ≥15% at doses of 3.8gram and 4.5gram daily. However, only a limited number of the patients reached the clinically more relevant target of LDL cholesterol <3mmol/L. More than 50% of patients achieved at least a 15% reduction in LDL cholesterol regardless of baseline figures. 6% and 14% of patients were non-responders in the colesevelam 3.8gram and 4.5gram group respectively. [4] Small but significant increases in HDL cholesterol were also noted.

Study GTC-48-302 was a randomised, double-blind, parallel design, placebo-controlled pivotal phase III dose regimen study. The intention of the study was to assess safety and efficacy of once daily dosing of colesevelam. 98 patients with a previous diagnosis of primary hypercholesterolaemia were randomised to either the active drug or placebo, 75 received colesevelam and 23 received placebo. Participants in the active treatment group received colesevelam 3.8gram in the morning, 3.8gram given in the evening or 1.9gram given twice a day. The primary endpoint was the change in serum LDL-C from baseline to completion of the treatment period. The study lasted six weeks. [4]

90 participants (92%) completed the trial. Reductions in mean change and mean percentage change in LDL cholesterol were statistically significant for each of the active treatment groups. The changes in lipid parameters (LDL cholesterol, total cholesterol, triglycerides and HDL cholesterol) did not show statistically significant differences between the three colesevelam dosing regimens. [4]

Percentage change in LDL cholesterol was similar in the evaluable population with LDL reductions of 20%, 16% and 19% for morning, evening and twice daily treatment groups respectively. Triglycerides increased more in the morning dosing group than the evening dosing group. [4]

A variation assessment report was published by the EMA in 2010 following a submission by the manufacturer to extend the license of Cholestagel. [5] The EMA agreed the extension to the licensed indication to include use of colesevelam in combination with ezetimibe, with or without a statin, in adult patients with primary hypercholesterolaemia, including patients with familial hypercholesterolaemia. The variation report considered two new studies: **CHOL00107** and **WEL408**. [5]

CHOL00107 was a phase IV randomised, double-blind, placebo-controlled, parallel-group, multicentre study of colesevelam as add-on therapy in patients with familial

hypercholesterolaemia. 86 patients were randomised to treatment groups: 45 were randomised to receive colesevelam and 41 to receive placebo. All patients were required to be on a stable maximally tolerated dose of statin treatment plus ezetimibe 10mg for minimum of three months before being screened for inclusion in the trial. The interpretation of maximally tolerated statin was based on the opinion of the treating physician. The EMA noted that the majority of patients (79%) received either a maximum authorised or maximum tolerated dose of statin for duration of on average 4.1 years and these doses exceeded those used in current clinical practice (circa 2010). The study lasted for 12 weeks. After the 12-week double-blind period, patients entered an open-label phase of the study. The primary endpoint of the study was the difference between colesevelam and placebo treatment groups for percentage change in LDL cholesterol from baseline at week six. The ITT population was used for the primary endpoint analysis with the per protocol population being used as a confirmative measure. The EMA stated that the statistical methods were sufficient to calculate treatment effects of the primary endpoint. [5]

Colesevelam, as add-on therapy to a maximally-tolerated and stable regimen of statin of ezetimibe, significantly reduced LDL cholesterol levels compared to placebo at week six as well as week 12 of treatment (week 12 assessment formed a secondary endpoint). Mean LDL cholesterol levels were 3.9mmol/L (standard deviation = 0.98) and 3.8mmol/L (0.98) at baseline in the colesevelam treatment and placebo groups respectively. At week six, defined by the primary endpoint, mean LDL cholesterol levels were 3.3mmol/L (0.78) in the colesevelam group and 4.0mmol/L (1.10) in the placebo group, a percentage change of -11.3% and +7.0% respectively. The difference in percentage change was -18.7% ($p < 0.0001$) in favour of colesevelam active treatment. Subgroup analysis showed that within each group of statins used, colesevelam showed a comparable additional LDL cholesterol reduction as seen as in the overall group of patients. [5]

At week 12, mean LDL cholesterol was 3.4mmol/L (0.81) and 3.8mmol/L (1.05) in the active and placebo groups respectively with a corresponding mean percentage change of -10.9% and +0.9%. The difference in percentage change was -11.8% ($p = 0.0001$) in favour of active treatment. The EMA concluded that despite high dose statin therapy and additional ezetimibe therapy, colesevelam reduced LDL cholesterol levels by 11% compared to placebo. [5]

WEL408 was a multi-centre, randomised, double-blind, placebo-controlled, parallel group study. The objectives of the study were: a) to compare the effect of colesevelam in combination with ezetimibe to ezetimibe alone on LDL cholesterol concentration in patients with primary hypercholesterolaemia and b) to compare the effects of colesevelam in combination with ezetimibe and simvastatin to ezetimibe in combination with simvastatin. [5]

Objective a) was also reported in a paper by **Bays et al, 2006**. [6] 119 participants with primary hypercholesterolaemia were enrolled in to the study and 86 were randomised to treatment

groups. The ITT population was 85 (one participant was excluded in the colesevelam and ezetimibe treatment group because of a missing fasting lipid assessment). Participants received either colesevelam 3.8gram daily plus ezetimibe 10mg daily or colesevelam placebo plus ezetimibe 10mg daily. The study lasted for ten weeks. The primary efficacy endpoint was mean percentage change in LDL cholesterol concentration at week six. [6] [5]

Of the 86 participants that were randomised to treatment, 43 received colesevelam plus ezetimibe and 43 received colesevelam placebo plus ezetimibe. 41 and 43 participants completed the six- week study in each group respectively. Compliance across both treatment groups was between 95 and 98%. Colesevelam plus ezetimibe and colesevelam placebo plus ezetimibe both resulted in significant mean decreases in LDL cholesterol levels compared with baseline (least squares % change from baseline [standard error] -32.3 [1.8] and -21.4 [1.8] respectively [both $p < 0.0001$]). Colesevelam in addition to ezetimibe resulted in an additional 11% reduction in LDL cholesterol levels from baseline to ezetimibe treatment and placebo. [6] [5]

Objective b) was tested by adding open-label simvastatin (20mg daily) to the participants existing, blinded and randomised, treatment regimen for an additional four-week period. [5] At week 10 there was no significant difference in LDL cholesterol levels between treatment groups. The active treatment group had a mean LDL cholesterol level of 75mg/dL (26) and a mean percentage change from baseline of -57%. The placebo group had a mean LDL cholesterol level of 85mg/dL (27) and a mean percentage change from baseline of -51%. The difference in percentage change between active and placebo colesevelam groups was -5.4% ($p = 0.099$). [5] The EMA observed that colesevelam should have been added to a combination of ezetimibe and simvastatin. They stated that drawing the conclusion that the addition of simvastatin to a combination of ezetimibe and colesevelam may reduce the effectiveness of colesevelam should be done with ‘care’. The EMA also pointed out that there were discrepancies between the trial evidence that was presented. It was also stated that the 11% mean reduction in LDL cholesterol levels was small but clinically relevant for the intended target population. [5]

Randomised Controlled Trials

Rosenson, 2006, published a double-blind, placebo-controlled, randomised trial. [7] The study focused on the reduction of LDL particle number and size in hypercholesterolaemia after treatment with colesevelam. 149 patients with moderate hypercholesterolaemia (LDL >4.14mmol/L and triglycerides <3.39mmo/L) were enrolled in to the study. Patients were randomised to receive either colesevelam 1.5gram to 3.75gram (four groups of participants received: 1.5gram, 2.25gram, 3.0gram and 3.75gram; groups sizes were broadly similar [either 29 or 30 participants]) daily or placebo. The primary endpoint to the study was change in LDL particle number and size, the study lasted for six weeks. LDL cholesterol concentration was a

significant secondary endpoint. [7]

LDL cholesterol concentrations were lower in the two groups that received the highest doses of colesevelam (3.0gram and 3.75gram daily) after six weeks (-9.5% [p = 0.0007] and -11.3% [p = 0.0001] respectively). Mean LDL particle size increased only at the highest dose of colesevelam (3.75gram daily; 1.1% increase in size [p = 0.01]). The authors stated that particle size was a weak predictor of cardiovascular risk. Mean LDL particle number was reduced by 6.8% (p = 0.03) in the 3.0gram daily and 13.7% (p = 0.0002) in the 3.75gram colesevelam treatment groups. The authors observed that subjects with low fasting triglycerides <2.26mmol/L and high fasting triglycerides ≥2.26mmol/L had similar reductions in mean LDL particle number across dosages however this observation was not significant (p = 0.18 – 0.62). [7]

Other efficacy data:

Davidson et al, 2010, published a 50-week extension study on the safety and efficacy of colesevelam in adults with primary hypercholesterolaemia. [8] The study was an open-label, multicentre, titration-based extension study. The study participants were recruited from three multicentre, randomised, double-blind, placebo-controlled, phase II studies with colesevelam. 260 participants were enrolled and 186 completed the study. The ITT population was used for the final efficacy analysis which was composed of participants that had received at least one dose of study medication and had one or more post-baseline lipid evaluation. All lipid-lowering medication was discontinued four weeks prior to the start of the study. Subjects initiated treatment at colesevelam 1.5gram daily and was up titrated to a maximum dosage of 3.75gram daily as necessary to achieve a 15 – 30% reduction from baseline in LDL cholesterol level. At week 12, a statin or nicotinic acid could be commenced if colesevelam 3.75gram daily was not sufficient to result in a 15 – 30% reduction. The primary efficacy endpoint was the change in LDL cholesterol level from baseline to week 50 across all treatment regimens.

The mean daily dose of colesevelam throughout the study was 2.80gram. During the final eight-weeks of the study the mean daily dose was 3.30gram. The maximum colesevelam dose (3.75gram daily) was reached by 50% of the study population who remained on colesevelam at week 50 (n=188). 38 participants received additional statin or nicotinic acid therapy by the end of the study. At week 50, LDL cholesterol levels were significantly reduced from baseline across all treatment regimens (-29.6mg/dL [185.8 – 156.2mg/dL; 15.0% reduction]; p < 0.001). The mean change from baseline of LDL cholesterol for those participants who received colesevelam monotherapy: all dosage regimens and maximum dosage regimen were lower: -10.9% (p < 0.001) and -12.9% (p < 0.001) respectively. The cohort of patients that received both colesevelam and statin therapy realised the greatest reduction in LDL cholesterol levels, mean change from baseline was -34.2% (p < 0.001). [8]

Summary of safety data:

Regulatory information

The summary of product characteristics (SPC) and EPAR documents both state that the chief adverse reactions are related to the gastrointestinal tract. Common adverse reactions that are not related to the gastrointestinal tract listed in the SPC are: headache and raised serum triglycerides. The EPAR stated that the rise in triglycerides is significant and caution is needed when treating patients with triglyceride levels >3.4mmol/L. [3] [4]

Colesevelam increases mean ALT, AST and ALP levels slightly when used alone. However, these adverse effects were predicted based on the known pharmacological action of the drug. These effects have also been reported in subsequent studies. Noted also was a small but significant decrease in the partial thromboplastin time (PTT). Therefore, caution should be excised when treating patients with susceptibility to vitamin K and other fat soluble vitamin deficiencies. Those receiving vitamin K antagonists, such as warfarin, should be monitored closely. [4] [8]

Interactions with other medicinal products

The SPC states that colesevelam may affect the bioavailability of other medicinal products. The SPC recommends that when a drug interaction cannot be excluded with a concomitant medicinal product for which minor variations in the therapeutic level would be clinically important, colesevelam should be administered at least four hours before or after the concomitant medication to minimise the risk of reduced absorption of the concomitant medication. [3]

Interaction studies have been completed in adults. Colesevelam had no effect on the bioavailability of digoxin, metoprolol, quinidine, valproic acid and warfarin. [3]

Colesevelam dereased the C_{max} and AUC or sustained release verapamil by approximately 31%. The clinical significant of this was unclear. Other medicinal products that interact with colesevelam, leading to reduced therapeutic levels are: olmesartan, phenytoin, vitamin k (consider vitamin K antagonists, such as warfarin), levothyroxine, oral contraceptive pill, ciclosposin, metformin, glimepiride, glipizide, glibenclamide and repaglinide. However, the SPC states that most of these can be reduced if co-administration of colesevelam and the medicinal product is avoided. [3]

RCT safety data

Bays et al, 2006, reported that participants taking active colesevelam plus ezetimibe experienced more adverse effects than those taking placebo plus ezetimibe (65.1% of participants versus 34.9%). The most common adverse events experience in both groups were gastrointestinal disturbances. There was one significant adverse reaction reported, a severe

case of diverticulitis which led to hospitalisation, the investigator deemed that this was not related to drug treatment. The patient had a previous history of diverticulitis. [6]

The study by **Rosenson, 2006**, did not include a discussion about the safety of colesevelam treatment.

Other safety data

Davidson et al, 2010, reported that adverse treatment reactions were reported by 225 participants (86.5%), with the majority of adverse events being classified as mild-to-moderate in severity. The most common adverse reactions not listed in the SPC were infection (reported by 28.5% of participants) and general pain (13.1%). 23 subjects discontinued therapy due to an adverse reaction, most were attributed to gastrointestinal adverse events. The remainder were due to: oedema, myocardial infarction, accidental injury, anaemia and depression and nervousness. These adverse events were considered either remotely related or unrelated to colesevelam. 21 serious adverse events were recorded, none of these were considered to be related to colesevelam. [8]

Strengths and limitations of the evidence:

Limitations

1. Limited numbers of post-licensing studies. There are two relevant post-licensing RCTs which were published, one of which had already been discussed by the EMA as part of the license extension for colesevelam. There was also one descriptive study. [6] [8] [7] [5]
2. Limited RCT data available in the literature – two relevant post-licensing RCT studies.
3. One RCT did not include power calculations. [7]
4. Study endpoints did not report patient-orientated outcomes. A surrogate measure, change in LDL cholesterol levels, were reported and reductions in cardiovascular events were not. [7] [8] [6]
5. Randomisation methods were not discussed in both RCTs that were discussed. Therefore, it is impossible to verify if allocation to treatment groups was free from bias. [6] [7]
6. High levels of adverse events; lack of safety analysis in one published RCT. [7]
7. The studies reviewed were of short duration. The two RCTs were six and ten weeks long. The open-label study was a 50-week study. Within the context of cardiovascular risk prediction and intended duration of therapy, in the case of FH life-long, these are relatively short studies and may not truly reflect long-term health gains. [6] [8] [7]

Strengths

1. All studies reviewed as part of the regulatory submission were of good quality. [11]
2. Colesevelam has been shown to reduce lipids. Colesevelam, when given as monotherapy, has been shown to reduce LDL cholesterol levels by up to 19% in short duration studies (6-

weeks) when given twice a day. [4] Longer-term studies (50-weeks) have shown colesevelam, as monotherapy, can reduce LDL cholesterol by between 10.9% ($p < 0.001$) and 12.9% ($p < 0.001$). [8] Further reductions are realised if colesevelam is used in combination with a statin. [4] [5] Cholestyramine monotherapy has been shown to reduced LDL cholesterol levels by 23% ($p < 0.001$) after 48 weeks of treatment. [11]

3. Colesevelam appears to be better tolerated than cholestyramine and cholestipol, although there are no comparison studies. There is some evidence in the literature to show that cholestyramine powder is poorly tolerated compared to cholestyramine tablets (25% improvement in compliance with regimen, tablets over powder [n = 16]; paediatric study [10 – 18years]). [12] However, there are no licensed tabletted forms of cholestyramine in the UK. Colesevelam is manufactured as tablets and appears to be better tolerated, compliance in one study was shown to be between 97% and 98%. [6]
4. The studies compared colesevelam with the following comparators:

Table 1 - Assessment of study interventions and comparators

Study	Intervention	Comparator	Primary outcome
Rosenson et al [7]	Colesevelam 1.5 – 3.75gram o.d. for six-weeks	Placebo	LDL particle number and size
Bays et al/WEL408 [6] [5]	Colesevelam 3.8gram o.d. plus ezetimibe 10mg o.d. for six-weeks	Colesevelam placebo o.d. plus ezetimbe 10mg o.d.	Mean percentage change in LDL cholesterol level during randomised treatment phase
Davidson et al [8]	Colesevelam monotherapy (all dose ranges) for 50-weeks	Colesevelam (all dose ranges) plus low dose statin or niacin therapy	Mean change in LDL cholesterol level from baseline to week 50
GTC-48-301 [4]	Colesevelam 2.3 – 4.5gram daily in divided doses for six-months	Placebo	Change in serum LDL cholesterol level from baseline to completion of treatment.
GTC-48-302 [4]	Colesevelam 1.9gram b.d., colesevelam 3.8gram mane or colesevelam 3.8gram nocte for six-weeks	Placebo	Change in serum LDL cholesterol level from baseline to completion of treatment.
CHOL00107 [5]	Colesevelam add on therapy to patients maintained on statin treatment and ezetimibe for twelve-weeks	Colesevelam placebo add on therapy to patients maintained on statin treatment and ezetimibe.	Difference between colesevelam and placebo treatment groups for percentage change in LDL cholesterol from baseline to week-six.

Different combinations of lipid-regulating drugs were either used in combination with active colesevelam, in order to determine additive effects, or used as a direct comparator. The trial evidence provides data that relates to clinically relevant combinations of drugs.

Measured

Summary of evidence on cost effectiveness:

No economic analysis relating to the use of colesevelam could be found in the literature.

Prescribing and risk management issues:

Colesevelam is a prescription only medicine and supply is subject to a prescription. There are no special precautions required for the storage of colesevelam.

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Colesevelam	**2.5gram – 4.375gram daily**	**180 x 625mg tablets = £96.10**	**£779.48 - £1364.31**
Cholestyramine	4gram – 36gram daily	50 x 4gram sachets= £31.85	£232.51 - £2092.54
Colestipol hydrochloride	5gram – 30gram daily	30 x 5gram sachets = £15.05	£183.11 - £1098.64
Costs based on BNF list prices 28/06/16 This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

It is not expected that additional outpatient clinic appointments will be required. There are no currently available manufacturer discounts.

Productivity, service delivery, implementation:

There is limited potential for increased demand in primary and secondary care services. Colesevelam

Anticipated patient numbers and net budget impact:

The applicants stated that they expected six patients per year to be treated with colesevelam in their organisation. The applicant serves roughly a third of the Lancashire foot print. Therefore, it can be reasonably expected that 30 patients would require treatment with colesevelam per year in Lancashire.

Data taken from NICE CG 71 shows the prevalence of heterozygous FH in the population is 0.2% (1 in 500). Across the Lancashire health economy, there are approximately 2,900 people living with FH. [2] However, it is estimated that only 15% of those with FH are identified within the population. Hence, approximately 435 patients within Lancashire are potentially accessing services for the management of FH. Further prevalence data is not available that can be used to derive estimated numbers of patients that would require second- and third-line treatment for FH

in Lancashire.
However, if all those accessing services for the treatment of FH required colesevelam, the potential budget impact to the Lancashire health economy would be £338,865 - £593,340 per year. Although, based on the applicant's estimate, **the cost of treating 30 patients at the maximum dose for one year would be £40,929.**

Innovation, need, equity:

Colesevelam is not an innovative new treatment. There are two bile acid sequestrants that are already available and are cheaper at the lower end of the dose range. There are no studies that use either cholestyramine or cholestipol as an active comparator versus colesevelam, although it is accepted that there are tolerability issues with the former two agents. [10] [12]
Colesevelam appears to be better tolerated than cholestyramine. Compliance with colesevelam in one study was shown to be between 97% and 98% (although in clinical practice this is likely to be lower). [6] Better tolerability could translate to improved concordance with therapy and better clinical outcomes because of this. However, there are no studies in the literature that measure patient centred outcomes, for example reduction in cardiovascular events, rather than surrogate measures, after exposure to colesevelam therapy.
The Midlands Therapeutics Review and Advisory Committee (MTRAC) did not recommended colesevelam for the treatment of primary hypercholesterolaemia because of the lack comparison studies with established bile acid sequestrants, the lack of longer-term data and the absence of patient centred outcomes in the published trials. MTRAC also concerned about binding of other drugs in the gut [13]

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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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