

Clinical Commissioning Policy Proposition: Cholic acid and chenodeoxycholic acid for treating inborn errors of bile acid synthesis (all ages)

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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 inborn errors of bile acid synthesis

Inborn errors of bile acid synthesis are a group of very rare conditions where the liver has difficulty making important substances called bile acids (such as cholic acid and chenodeoxycholic acid). Bile acids usually help to digest fats and aid vitamin absorption but, in people with inborn errors of bile acid synthesis, there is a problem with the proteins in the body that help with chemical reactions (enzymes needed for bile acid synthesis). Instead the liver makes too many unusual bile acids and substances known as metabolites (unfinished products of chemical reactions in the body that would usually be broken down). These substances can then build up in the liver and damage it. Inborn errors of bile acid synthesis can interfere with the body's ability to absorb enough of the fats and vitamins that it needs to be healthy, and can cause liver disease, cirrhosis (scarring of the liver), liver failure and death. In some cases, inborn errors of bile acid synthesis can cause progressive diseases of the central nervous system (affecting the brain and how people move).

There are many different types of inborn errors of bile acid synthesis. The age of diagnosis, symptoms, and outlook for the disease varies from person to person and depends on the particular type that a patient has. Principle types include:

- 3beta-HSD deficiency
 - People with this deficiency often develop cholestasis (reduced flow of bile from the liver), have problems with absorbing enough vitamins (which causes further health problems) and if the disease is untreated it can lead to progressive liver disease.
- 5beta-reductase deficiency
 - This causes problems similar to the deficiency above, but more severe and, if untreated, can quickly progress to cirrhosis and liver failure.
- AMACR deficiency
 - This can cause cholestasis and vitamin deficiency in babies. Older children and adults may develop symptoms such as numbness, 'pins and needles', weakness, and balance issues, because of damage caused to the nerves.
- CTX (cerebrotendinous xanthomatosis, also known as sterol 27-hydroxylase deficiency)
 - This causes increases in cholestanol (a substance similar to cholesterol) which can then collect in the body. This can cause damage to the brain, spinal cord, tendons, eyes and arteries. This includes some people getting cataracts (cloudy patches in the eye affecting sight) and diarrhoea during childhood and xanthomata (fatty deposits around the tendons) as teenagers. If untreated, it can cause worsening neurological problems in adulthood, potentially causing paralysis, ataxia (loss of control of body movements), and dementia. Coronary heart disease is also common. CTX can cause liver disease in babies but it is usually self-limiting.
- CYP7A1 deficiency
 - People with this deficiency have increased levels of cholesterol including total cholesterol and low-density lipoprotein cholesterol (LDL, or "bad", cholesterol), gallstones, and early onset of diseases of the heart and veins. People with this type usually do not have liver disease.

These conditions are genetic, the 'faulty genes' that are responsible for making enzymes are inherited, usually 1 faulty gene from each parent.

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

About current treatments

Inborn errors of bile acid synthesis are usually treated by replacing the missing bile acids, with a tablet taken orally. These acids may stop the disease from worsening or sometimes prevent symptoms from occurring if they have not already developed. The earlier treatment is started, the better the outcomes for patients. The bile acid taken will depend on the subtype of the disease, and it will typically be either chenodeoxycholic acid or cholic acid or a combination of the 2.

About the new treatment

As described above, treatment with chenodeoxycholic acid and cholic acid replaces the missing bile acids which can help stop symptoms appearing or prevent them from getting worse.

The choice of treatment will depend on the particular type of inborn error that the person has:

- For people with CTX
 - Chenodeoxycholic acid will be available as the first line treatment.
 - Cholic acid will be available as a second line treatment, if chenodeoxycholic acid is no longer tolerated or effective.
 - A combination of the 2 may be considered if cholic acid monotherapy is not effective (this is an off-label use of the 2 drugs)
- For people with all 4 other inborn errors of bile acid synthesis described in this document (deficiencies in: 3beta-HSD, 5beta-reductase, AMACR and CYP7A1)
 - Cholic acid will be available as a first line treatment.
 - A combination of cholic acid plus chenodeoxycholic acid 2 may be considered if cholic acid monotherapy is not effective (this is an off-label use of the 2 drugs)

What we have decided

NHS England has carefully reviewed the evidence to treat inborn errors of bile acid synthesis with cholic acid and chenodeoxycholic acid both within their licensed indications and off label (where 1 cholic acid product is used within the alternate cholic acid product's licence and where cholic acid is used in combination with chenodeoxycholic acid). We have concluded that there is enough evidence to consider making these treatments available.

2 Introduction

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

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 cholic acid and chenodeoxycholic acid 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

Bile acids are produced by the liver from cholesterol through a complex series of reactions involving at least 14 enzymatic steps. Inborn errors of bile acid synthesis are a group of rare genetic conditions where there is an enzyme deficiency stopping “normal” bile acid production, and instead high concentrations of unusual bile acids or bile alcohols and intermediary metabolites (some of which can be toxic to the liver) are produced. These conditions are rare genetic disorders caused by mutations in specific genes that are passed down to a child from each parent (autosomal recessive inheritance).

People with inborn errors of bile acid synthesis may present with cholestasis (interruption or suppression of the flow of bile from the liver), fat-soluble vitamin malabsorption and liver disease. Progressive neurological disease can also develop, even in the absence of liver disease. In addition, people may have complications such as rickets, susceptibility to bleeding (bleeding diathesis), night blindness (nyctalopia) and progressive neurological disease that affects movement and cognitive skills. If untreated, the more severe forms of these disorders can eventually progress to cause life-threatening complications such as scarring of the

liver (cirrhosis) and liver failure. The exact presentation of disease depends on the specific enzyme deficiency that the person has. Subtypes include:

- 3β -Hydroxy- Δ^5 -C27-steroid oxidoreductase deficiency (also called 3beta-HSD deficiency). People develop cholestasis and fat-soluble vitamin malabsorption during infancy (which then leads to a number of problems because of vitamin deficiency). Progressive liver disease occurs if the disease is not treated.
- Δ^4 -3-Oxosteroid- 5β -reductase deficiency (also called 5beta reductase deficiency). This presents in a similar way to 3beta-HSD deficiency, but more severe. Cirrhosis (where normal tissue is replaced by scar tissue in the liver) and liver failure can occur within a short space of time if the disease is not treated.
- Sterol 27-hydroxylase deficiency (also called cerebrotendinous xanthomatosis [CTX]). This causes an accumulation of cholestanol (a substance similar to cholesterol) in nerve cells and membranes. This can cause damage to the brain, spinal cord, tendons, lens of the eyes and arteries. Children with this deficiency can develop cataracts and diarrhoea during childhood and teenagers can develop xanthomata (fatty deposits in) the tendons. If untreated, progressive neurological problems develop in adulthood potentially causing paralysis, ataxia, and dementia. Coronary heart disease is also common. The mean age of diagnosis of CTX has been reported as around 35–37 years, by which time there is often significant neurological involvement. CTX can cause liver disease in babies but it is usually self-limiting.
- 2- (or α -) methylacyl-CoA racemase deficiency (AMACR). People may present with sensory motor neuropathy which causes abnormal sensations, such as numbness (or “pins and needles”), muscle weakness, and problems with balance and coordination. In some adults, they may have had liver disease during childhood, or symptoms might not develop until there is sensory motor neuropathy in adulthood. In some infants, the condition presents with severe fat and fat-soluble vitamin deficiencies and mild cholestasis.

- Cholesterol 7 α -hydroxylase deficiency (CYP7A1). People develop elevated levels of total and LDL cholesterol, premature gallstones, and premature coronary and peripheral vascular disease. People do not usually have liver disease.
- *(source for all the above: National Organization for Rare Disorders: Bile acid synthesis disorders)*

Symptoms are often present at birth or during infancy, but the diseases affect people of all ages and the age of onset, specific symptoms, and rate of progression can vary greatly from 1 person to another depending on the specific underlying defect. The most common inborn errors of primary bile acid synthesis are 3 β -HSD deficiency and 5 β -reductase deficiency, in which primary acid synthesis is absent or negligible (Heubi et al. 2017).

Inborn errors of bile acid synthesis are usually treated by replacing the main missing bile acids (cholic acid and chenodeoxycholic acid) using a tablet containing the relevant bile acid, taken orally. The bile acid taken will depend on the subtype of the disease. Cholic acid and chenodeoxycholic acid have been used as standard of care for this population in NHS practice for many years. They have also been used in combination (Subramaniam et al. 2010). CTX has been treated with chenodeoxycholic acid for over 40 years, with “objectively measurable significant improvements in metabolic and clinical parameters” ([European public assessment report \(EPAR\) for chenodeoxycholic acid](#)). Cholic acid is also licensed for people with CTX, and it can be effective in improving biochemical outcomes. However, it is not as effective as chenodeoxycholic acid “in suppressing BAS and the production of cholestanol” ([Orphanet monograph for CTX](#)), and there is no long term effectiveness evidence for the neurological aspect of the disease. All other subtypes considered in this draft policy proposition are typically first treated with cholic acid.

Treatment with cholic acid and chenodeoxycholic acid can stop disease progression (if a patient is symptomatic, cessation of the natural progression of disease is often a positive outcome for patients), or even sometimes prevent symptoms from occurring if they have not already developed. Evidence suggests

earlier treatment allows the opportunity to stop progression of disease sooner, leading to better outcomes for patients, for example:

- In children, prompt treatment with bile acids can lead to regression or sometimes resolution of liver disease (Subramaniam et al. 2010).
- People with CTX who started treatment with chenodeoxycholic acid after the age of 25 years have shown worse outcomes, with more limited ambulation and cognitive impairment than those who started treatment before the age of 25 years. (National Organization for Rare Disorders: Cerebrotendinous xanthomatosis).

Other treatments have been tried for people with inborn errors of bile acid synthesis. Ursodeoxycholic acid has been used for the 5 β -reductase subpopulation, however it is not licensed for this indication, there is no evidence for its use ([BNF inborn errors of primary bile acid synthesis treatment](#)) and it does not suppress atypical bile acid synthesis, leaving continued production of toxic metabolites (Orphanet monograph for AMACR deficiency). Nutraceuticals (such as ox bile) can contain the bile acids necessary for treating inborn errors of bile acid synthesis, but they are not licensed treatments therefore are not regulated with the same level of rigour as licensed treatments.

Chenodeoxycholic acid has a licence for the “treatment of inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis, or CTX) in infants, children and adolescents aged 1 month to 18 years and adults”.

There are 2 proprietary versions of cholic acid (Orphacol and Kolbam) with licenses as follows:

- Orphacol has a licence for the “treatment of inborn errors in primary bile acid synthesis due to 3 β -Hydroxy- Δ 5-C27-steroid oxidoreductase deficiency or Δ 4-3-Oxosteroid-5 β -reductase deficiency in infants, children and adolescents aged 1 month to 18 years and adults”.
- Kolbam has a licence for the “treatment of inborn errors in primary bile acid synthesis due to sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α -) methylacyl-CoA racemase

(AMACR) deficiency or cholesterol 7 α -hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults".

Please note that Kolbam has not launched officially in the UK ([Specialist Pharmacy Service: Cholic acid](#)), but it does have a European licence and data suggests it has been used in England.

4 Definitions

Areflexia – absence of tendon reflexes.

Ataxia – loss of control of bodily movements.

Autosomal recessive inheritance – both copies of a gene have to be mutated to cause disease, with 1 copy usually coming from each parent.

Bile – fluid produced by the liver that helps to digest fats.

Bile acids – are detergents in bile (the human primary bile acids are cholic acid and chenodeoxycholic acid).

Cerebrotendinous xanthomatosis (CTX) – a rare genetic disorder in which an enzyme deficiency (sterol 27-hydroxylase deficiency) prevents cholesterol from being converted to chenodeoxycholic acid.

Cholestanol – a substance in the body that is derived from cholesterol, which can build up in people with CTX and damage their organs.

Cholestasis – interruption or suppression of the flow of bile from the liver, which can cause jaundice, malabsorption and liver problems.

Cholesterol – an important type of fat or lipid in the body, which is used to produce substances such as bile acids, vitamins and hormones.

Cirrhosis – a serious condition of the liver where normal liver tissue is replaced by scar tissue.

Enzyme – a protein that helps to produce a chemical reaction in the body.

Expanded Disability Status Scale (EDSS) – a tool used to rate a person's level of disability.

Hepatomegaly – liver enlargement.

Icterus – yellow discoloration of the skin, see also jaundice (adjective; icteric).

Inborn errors of primary bile acid synthesis – rare genetic disorders that lead to deficiencies in enzymes that are needed for the liver to convert cholesterol in the body to bile acids.

Intermediary metabolites – substances that would usually be broken down by enzymes.

Jaundice – yellowing of the skin, mucous membranes and whites of the eyes.

Malaise – feeling of weakness or discomfort.

Peroxisomal disorders – disorders caused by defects in peroxisome functions.

This may be due to defects in single enzymes important for peroxisome function or in peroxins, proteins encoded by PEX genes that are critical for normal peroxisome assembly and biogenesis

Rankin scale – a tool used to rate a person's level of disability and dependence.

Single enzyme deficiency – refers to inborn errors of primary bile acid synthesis caused by deficiencies in one of the following enzymes; 3beta-HSD), 5beta-reductase), AMACR, sterol 27-hydroxylase and CYP7A1.

Steatorrhea – fatty stools.

Zellweger spectrum disorders – types of peroxisomal disorder.

5 Aims and Objectives

This policy proposition considered: cholic acid for treating inborn errors in primary bile acid synthesis due to 3beta-HSD deficiency, 5beta-reductase deficiency, CTX, AMACR deficiency or CYP7A1 deficiency, and; chenodeoxycholic acid for CTX.

The objectives were to:

- Define the eligibility criteria for cholic acid and chenodeoxycholic acid.
- Define the commissioning arrangements required for cholic acid and chenodeoxycholic acid.

6 Epidemiology and Needs Assessment

Inborn errors of bile acid synthesis are very rare, and there are limited data available on incidence and prevalence, particularly for specific subtypes. The EPAR for Kolbam states the prevalence of people with inborn errors of bile acid synthesis in the EU is 0.07 per 10,000. A bibliographic study of the epidemiology of rare diseases estimated that there are about 200 people in Europe with CTX (EURODIS and ORPHANET: Rare diseases in numbers). NHS England data suggests that 26 patients with CTX are currently being treated with chenodeoxycholic acid, there are

3 patients awaiting treatment and the company for chenodeoxycholic estimates that there are 2 children with CTX currently being treated with Kolbam (cholic acid). Therefore the population group is estimated to be 30.

The prevalence of 3beta-HSD and 5 beta-reductase deficiency is estimated to be 4.4 cases per million (derived using the mid-point of assumptions from the Orphacol SPC) which equates to 24 people in total. NHS England data suggests this rate is slightly higher in England at around 4.8 per million, plus 1 patient awaiting treatment, equating to 28 patients overall (22 adults and 6 children).

AMACR (less than 10 cases in literature, National Organization for Rare disorders) and CYP7A1 (approximately 24 people worldwide, EURODIS and ORPHANET: Rare diseases in numbers) subtypes are particularly rare.

In summary, the total eligible population for both drugs in England is approximately **60** people, based on:

- CTX: 30 people
- 3beta-HSD deficiency and 5beta reductase deficiency: 28 people
- AMACR: unknown, but unlikely to be more than 1 person
- CYP7A1: unknown, unlikely to be more than 1 person.

7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of the treatments for their licensed indications.

Chenodeoxycholic acid (see NICE Clinical evidence review of chenodeoxycholic acid for treating cerebrotendinous xanthomatosis)

Included studies

The evidence review primarily considers the results of 2 small retrospective cohort studies (n=35 and n=28) that were considered by the European Medicines Agency during the regulatory process for the authorisation of chenodeoxycholic acid (see the [European public assessment report](#) (EPAR)). It also includes a smaller study by

[del Mar Amador et al. \(2018\)](#) (n=14) and outlines a literature review included in the EPAR (39 case series and 31 single case reports, n=204).

When interpreting this evidence, it is important to take the following limitations into account. There have been no prospective, controlled clinical studies of chenodeoxycholic acid in CTX and the rarity of the condition makes higher quality studies difficult. The studies included in the evidence review are small (n=35, n=28 and n=14), uncontrolled, retrospective studies, therefore their results should be interpreted with caution. Data were commonly missing across the time points, and most outcomes in the 2 larger studies were reported as improved, stabilised or deteriorated but these are not defined. Compliance with treatment was not reported. Post treatment assessments were at different intervals for each of the participants. Also, many people received additional treatments as well as chenodeoxycholic acid, which may disguise the true effect of chenodeoxycholic acid. The studies' design and conduct mean they are subject to bias and confounding, are difficult to interpret, and cannot support firm conclusions.

There are no comparative studies for chenodeoxycholic acid. However, there is some limited evidence from non-comparative studies where people took other treatments for CTX. These suggest that ursodeoxycholic acid is 'ineffective' for reducing serum cholestanol and urinary bile alcohols ([Koopman BJ et al. 1988](#)). For example, [Berginer et al. \(1984\)](#) studied the effects of chenodeoxycholic acid in 17 people. When 2 people, who had been treated successfully with chenodeoxycholic acid, switched treatment to ursodeoxycholic acid, their plasma cholestanol levels rose to pre-treatment levels. In a study of 20 people, [Waterreus et al. \(1987\)](#) reported that there were no changes in urinary bile alcohol levels or serum cholestanol/cholesterol ratios in 2 people who took ursodeoxycholic acid.

Clinical effectiveness

Serum cholestanol and urinary bile alcohol levels

In people with CTX who were treated with chenodeoxycholic acid in the main retrospective study (CDCA-STUK-15-001, n=35, mean duration of treatment 10.74 years), there were statistically significant improvements in mean serum cholestanol (a substance in the body, which can build up in people with CTX and

damage organs) and urinary bile alcohol levels (these are higher than normal in people with CTX; although this outcome does not have a tangible impact for patients, it helps to show how much the treatment is controlling the disease by demonstrating whether it is effective on a biochemical level). Statistically significant improvements in mean serum cholestanol levels were also seen in people who were treated with chenodeoxycholic acid in the second, supportive retrospective study considered by the European Medicines Agency (CDCA-STRCH-CR-14-001, n=28, median follow-up 5.75 years) and the study by del Mar Amador et al. (n=14, mean follow-up 5 years). The reduction in the build-up of these substances suggests that replacement treatment with chenodeoxycholic acid may correct for the inadequate production of this bile acid and reduce the production of toxic compounds such as cholestanol, although these results should be interpreted with caution because of the limitations of the evidence (see above).

Neurological disability and dependence

Neurological disability and dependence was measured using 2 scales (the [Rankin Scale](#) and the [Expanded Disability Status Scale](#) [EDSS]) in the 2 larger studies. In the main study, scores on both scales remained stable or improved between baseline and the most recent clinical current visit in about 80% of people. In the supportive study, scores remained stable in about 60% and 50% of people when the Rankin scale and EDSS were used respectively. Overall, there was a statistically significant worsening of the mean Rankin and EDSS scores from baseline in the supportive study, but not in the main study. The study by del Mar Amador et al. also considered EDSS scores. It found that, overall, mean scores remained stable.

Results suggest that chenodeoxycholic acid may reduce the deterioration in these scores, with the chances of success increasing in younger people, who were at an earlier stage of the disease. However, results were reported as improved, stabilised or deteriorated, but these are not defined, making these results difficult to interpret.

Clinical signs and symptoms

Generally, signs and symptoms of CTX resolved, improved or remained stable in most people over the course of the main study. For example, diarrhoea resolved in everyone who had this symptom at baseline and cognitive impairment resolved, improved or remained stable in everyone with this symptom. In the supportive study, signs and symptoms of the disease remained stable in most people, although fewer people saw positive outcomes than in the main study and some deteriorated. The poorer outcomes in the supportive study may be because people in this study were, on average, older and had higher disability scores at baseline. Few clinical outcomes were assessed by del Amador et al.

In the literature review, included in the EPAR, biochemical outcomes improved in 100% of people. Also, more than 70% of people experienced stabilisation or improvement in clinical outcomes.

In summary, the studies suggest that replacement therapy with chenodeoxycholic acid may normalise the results of certain laboratory tests, and can improve or, more often, stabilise symptoms of CTX, particularly in younger people with lower disability scores. However, results were reported as improved, stabilised or deteriorated, but these are not defined, making these results difficult to interpret.

Safety

According to the [summary of product characteristics](#), the adverse effects of chenodeoxycholic acid are generally mild-to-moderate in severity, transitory and do not interfere with the therapy.

In the main study, only 3 treatment-related adverse events were seen. These were constipation in 2 people and toxic hepatitis in 1 person, which were not considered to be serious. No treatment-related adverse events were seen in the supportive study, and treatment was reported to be 'well tolerated' in people in the study by del Mar Amador et al.

Cholic acid (see NICE Clinical evidence review of cholic acid for treating inborn errors of primary bile acid synthesis)

There are 2 proprietary versions of cholic acid, both of which contain the same active substance, but have different licensed indications (see section 3). The evidence for cholic acid as a whole has been presented, unless otherwise specified.

Included studies

The evidence for the efficacy and safety of cholic acid comes from 3 published studies and 1 unpublished study that was reported in the EPAR for Kolbam. Data from literature reviews included in the EPARs for Orphacol and Kolbam were also used as part of the evidence review to supplement the included studies because of the low numbers of people reported in the studies with the single enzyme deficiencies in question. Most people included in the studies had 3beta-HSD deficiency (n=80), followed by 5beta-reductase deficiency (n=19), CTX (n=9), AMACR deficiency (n=1) and others/unknown (n=3). The EPAR for Kolbam (which is licensed in sterol 27-hydroxylase, AMACR and CYP7A1 deficiencies) states that the conclusion of therapeutic efficacy is made considering results across all single enzyme deficiencies included in the trial (this included people with 3beta-HSD and 5beta-reductase deficiencies). Therefore results were not generally reported by subtype, and the subtypes had uneven representation across and within studies.

The main study was reported by [Heubi et al 2017](#), (study CAC-91-10-10) which was a phase 3, open-label, single-arm, non-randomised, compassionate treatment study that included 54 people (mean age of 3 years at the start of treatment) with single enzyme deficiencies (intention to treat population figures used) studied over an 18-year period. There were 2 [prospective](#) observational studies reported by [Al-Hussaini et al 2017](#) and [Gonzales et al. 2009](#), each included 15 people with 3beta-HSD and 5beta-reductase deficiencies followed-up over 10 years and median follow-up of 12.4 years respectively. The unpublished study was a continuation study (study CAC-002-001) of the study reported by Heubi et al. 2017. The continuation study was conducted over 33 months and included 29 people with single enzyme deficiencies (recruited people from the main study and new people). Data included from the literature review from the EPARs were from

small studies of people with single enzyme deficiencies that were case reports or reports of siblings treated with cholic acid monotherapy.

When interpreting this evidence, it is important to take the following limitations into account. The main evidence for cholic acid comes from uncontrolled open-label [observational studies](#) which are of a low-quality and have many limitations that affect its application to clinical practice. Observational studies have limitations inherent in their non-[randomised](#) design, especially around [bias](#) and [confounding](#) variables (including demographic and environmental factors, duration of disease and comorbidities). In these studies, outcome assessments were not [blinded](#), which is another potential source of bias. The studies included small numbers of people (the EPAR for Kolbam states the following about the population covered by the Kolbam licence: “Given the rarity of the diseases, the CHMP considered that the applicant cannot be reasonably expected to provide comprehensive non-clinical and clinical evidence”), which limits its ability to detect effectiveness and adverse effects of treatment. Some people received additional treatment with ursodeoxycholic acid as well as cholic acid, which may disguise the true treatment effect of cholic acid.

Clinical effectiveness

Atypical urinary bile acids

Atypical urinary bile acids are markers of incomplete metabolism, which can be associated with liver disease. In the main study by Heubi et al. 2017, there was a statistically significant decrease in the percentage of people with marked abnormalities in atypical bile acid score after treatment with cholic acid (72.1% pre-treatment compared with 14% post-treatment, $p < 0.0001$). Improvements in the amount of atypical bile acids in people's urine was supported by all other included studies and by the literature review reported in the EPARs for cholic acid (Orphacol and Kolbam). The results suggest treatment with cholic acid reduces the amount of atypical bile acids in the urine.

Liver function

People with inborn errors of primary bile acid synthesis produce abnormal bile acids that can be toxic to the liver and affect the way it works. Liver function was measured using serum transaminases, which were found to improve after treatment with cholic acid compared with pre-treatment in all the studies. The main study found a statistically significant improvement in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels from before to after treatment with cholic acid. Improvements in liver function was supported by 3 other studies and by the literature review reported in the EPARs for cholic acid (Orphacol and Kolbam). Liver histology was also reported in the literature review. According to the EPAR for Orphacol, where data was available in the literature review, a resolution of liver pathology was found in some while fibrosis (mild or septal) remained in others, during treatment with cholic acid. Results from the studies suggest treatment with cholic acid may improve liver function in people with inborn errors of bile acid metabolism, although the limitations of the evidence base should be considered when interpreting this outcome.

Height and weight

Height and weight were both reported to have increased after treatment with cholic acid compared with baseline in 3 studies, however a statistically significant improvement in weight only, was reported by the main study. Results suggest that treatment with cholic acid may help to improve growth in people with inborn errors of bile acid metabolism, although the limitations of the evidence base should be considered when interpreting this outcome.

Clinical features

Clinical features such as hepatomegaly (enlargement of the liver), steatorrhea (fatty stools) and areflexia (absence of tendon reflexes) were reported to have clinically improved after treatment with cholic acid compared with pre-treatment in the study by Gonzales et al. 2009. There was a statistically significant improvement in the number of people with steatorrhea after cholic acid treatment in this study. Al-Hussaini et al. 2017 found an improvement of clinical features during cholic acid treatment compared with pre-treatment, however the significance of clinical improvement was not reported in the study and also the

term 'improvement' was not clearly defined. Results suggest that treatment with cholic acid may improve some of the clinical features in people with inborn errors of primary bile acid synthesis.

Response to cholic acid treatment

Response to cholic acid treatment was measured by looking at the number of people with cholestasis (interruption or suppression of the flow of bile from the liver) and liver dysfunction before and after cholic acid treatment, and also assessing how many people survived with their own liver. The study by Al-Hussaini et al. 2017 reported this outcome and found that the number of people with cholestasis and liver dysfunction improved after starting cholic acid treatment compared with pre-treatment. Eleven out of 15 people were reported to survive after a median follow-up period of 4.5 years, 10 of these had their own liver and 1 had a liver transplant. Data from the literature review showed that people treated with cholic acid were less likely to need a liver transplant when compared with untreated people or siblings with the condition. Although the results are supported by the data in the literature review, it is unclear in the study by Al-Hussaini et al. 2017 whether treatment with cholic acid affected survival and the need for a liver transplant because there was no control to compare this with. As there was no numerical data provided in the study, it is not known if treatment with cholic acid affected cholestasis and liver dysfunction.

Safety

Results from the studies showed that the adverse effects of cholic acid were generally mild-to-moderate in severity, did not interfere with the therapy, and resolved after reducing dose.

The number of people who stopped taking cholic acid treatment was 3 people in the main study and 4 people in the continuation study. The most common reason for stopping treatment was because of disease progression and not thought to be related to cholic acid treatment.

The number of people who died during cholic acid treatment was 7 people in the main study and 4 in Al-Hussaini et al. 2017. None of the adverse events leading to death was thought to be related to cholic acid treatment.

Cholic acid and chenodeoxycholic acid in combination (see NHS Evidence Review: Bile acid replacement therapy for inborn errors of bile synthesis)

The combination of chenodeoxycholic acid with either of the cholic acid preparations is considered off label.

Included studies

Six papers were included in this review. All were uncontrolled case studies or small case series, most reporting results in children. Three reported results of bile acid replacement in Δ^4 -3-oxosteroid 5 β -reductase deficiency (Daugherty 1993 (2 children), Clayton 1996 (1 child) and Lemonde 2003 (1 child)), 1 reported results in 2 children with Smith-Lemli-Opitz syndrome (Nwokoro 1997), 1 reported results in a child with Zellweger syndrome (Setchell 1992) and 1 reported results in an adult with 3 β -hydroxy- Δ^5 -C₂₇-steroid dehydrogenase deficiency (Nittono 2010).

All 6 studies reported results of liver function tests, and 4 also reported urinary bile acid concentrations. No other results were reported.

Clinical effectiveness

Liver function tests

Three studies reported changes in serum concentrations of alanine transaminase (ALT). Nittono et al (2010) reported a reduction in their patient's serum ALT from 45 IU/l before treatment with cholic acid and chenodeoxycholic acid, to 10 IU/l on treatment (normal range 5 to 45 IU/l). Lemonde et al (2003) reported a reduction in 1 patient's serum ALT from 1702 IU/l before treatment with cholic acid and chenodeoxycholic acid, to 184 IU/l on treatment (same normal range). Both patients reported by Daugherty et al 1993 had a normal ALT concentration before and after treatment.

Five studies reported changes in serum bilirubin concentrations. Nittono et al (2010) reported that total bilirubin fell from 6.8 mg/dl before treatment to 0.94 mg/dl

on treatment (normal range 0.2 to 1.1 mg/dl). Lemonde et al (2003) reported a reduction in 1 patient's serum bilirubin from 446 $\mu\text{mol/l}$ before treatment with cholic acid and chenodeoxycholic acid, to 117 $\mu\text{mol/l}$ on treatment (normal range not stated). Clayton et al (1996) reported a reduction in their patient's serum bilirubin from 88 $\mu\text{mol/l}$ before treatment with cholic acid and chenodeoxycholic acid, to 5 $\mu\text{mol/l}$ on treatment (normal range not stated, results estimated from graphs and hence approximate). One twin in Daugherty et al's study had an unchanged bilirubin concentration of 20 mg/dl before and after treatment, while the other had values of 20 mg/dl and 23 mg/dl respectively (normal range 0 to 1.8 mg/dl). Setchell et al (1992) reported that the infant in their study had a total bilirubin concentration before treatment of 3.2 mg/dl, at 3 months of 1.1 mg/dl, at 6 months of 0.8 mg/dl and at 8 months of 0.5 mg/dl (normal range not stated).

Urinary bile acid concentrations

Two studies reported total urinary bile acid concentrations. Daugherty et al (1993) reported that one of the twins in their study had a concentration before treatment of 46 $\mu\text{mol/l}$, and after treatment of 40 $\mu\text{mol/l}$; the other twin's results were 23 $\mu\text{mol/l}$ and 70 $\mu\text{mol/l}$ respectively (normal ranges not reported). The infant reported by Setchell et al (1992) had total urinary bile acids before treatment of 27.8 $\mu\text{mol/l}$, on day 1 of 104 $\mu\text{mol/l}$, on day 7 of 155 $\mu\text{mol/l}$ and on day 10 of 119 $\mu\text{mol/l}$ (normal ranges not reported).

None of the studies used tests of statistical significance to assess whether chance might explain their findings.

Taken together, the studies are consistent with improvements in liver function after the introduction of combination treatment with cholic acid and chenodeoxycholic acid, compared with results before treatment. However, the evidence was scanty, with no information about the effects of this treatment on symptoms, disease progression, liver transplant rates or survival. The available evidence does not allow any comparisons to be made between combination treatment with cholic acid and chenodeoxycholic acid, and any other treatment.

Safety

The literature search found no evidence comparing the safety of combination treatment of cholic acid and chenodeoxycholic acid with that of any other treatment. However, it can be assumed that the combination is as well tolerated as when the products are used as monotherapy.

8 Proposed Criteria for Commissioning

Chenodeoxycholic acid

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

Patients have a confirmed diagnosis of sterol 27-hydroxylase enzyme deficiency using biochemical evidence, and genetic evidence where this is accessible:

- Biochemical evidence:
 - Marked elevation of plasma cholestanol, OR
 - Marked elevation of urine or plasma bile alcohols, OR
 - Presence of other intermediates in primary bile acid biosynthesis including 7 α -Hydroxy-4-cholesten-3-one, 7 α ,12 α -dihydroxy-4-cholesten-3-one
- Genetic evidence
 - Genetic confirmation of *CYP27A1* mutations.

AND

The treatment decisions must be initiated, and monitored, by physicians experienced in the management of CTX or inborn errors of primary bile acid synthesis. This should include both a consultant specialising in inborn errors of metabolism, and/or a neurologist for paediatrics or adults.

AND

At baseline, all patients should receive a recording of the following (to monitor disease progression, and treatment effectiveness at follow-up appointments), as long as clinically appropriate:

- Plasma cholestanol
- Plasma bile alcohols
- Urinary bile alcohols
- Plasma 7 α -hydroxy-cholest-4-en-3-one
- Neuroimaging using MRI
- Clinical features of disease (will vary depending on disease manifestation in individual patients, but appropriate measures include liver disease, diarrhoea, growth, xanthomata, ataxia, neuropathy, and psychiatric and neurological outcomes)
- Age-appropriate full neuropsychological assessment

Stopping criteria (chenodeoxycholic acid)

Stop treatment with chenodeoxycholic acid if, after confirming patient compliance with treatment and appropriate dose adjustment, treatment is not effective.

Effectiveness measured using improvement or stabilisation in neuropsychological assessment results or neuroimaging results from MRI, plus 1 of the following:

- Plasma cholestanol
- Plasma or urinary bile alcohols
- Plasma 7 α -hydroxy-cholest-4-en-3-one
- Clinical features of disease (will vary depending on disease manifestation in individual patients, but appropriate measures include liver disease, diarrhoea, growth, xanthomata, ataxia, neuropathy, and psychiatric and neurological outcomes)

OR

If there are adverse effects of treatment:

- ADJUST DOSE if
 - Clinically significant deterioration in liver function assessed by:
 - Elevation of serum gamma glutamyltransferase (GGT), alanine aminotransferase (ALT) and/or marked elevation of serum bile acids above baseline levels, OR
 - Prolongation of prothrombin time

- **STOP TREATMENT** if there is persistent worsening of the above tests despite dose adjustment.

Effectiveness and safety measures should be monitored 3-monthly during the first year, and annually thereafter. Additional or more frequent investigations should be undertaken to monitor therapy during periods of fast growth, concomitant disease and pregnancy, or if there are deranged liver tests.

Cholic acid

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

For people with the following inborn errors of bile acid synthesis: 3beta-HSD, 5beta-reductase, AMACR and CYP7A1

Patients have a confirmed diagnosis of one of the following inborn errors of bile acid synthesis: 3beta-HSD, 5beta-reductase, AMACR and CYP7A1, using biochemical evidence, and genetic evidence where this is accessible:

- Biochemical evidence of atypical blood or urinary bile acids or alcohols, consistent with the appropriate deficiency, using techniques such as electrospray ionisation mass spectrometry
- Genetic testing of the relevant gene.

AND

At baseline, all patients should receive a recording of clinical features of disease, plus the following (to monitor disease progression, and treatment effectiveness, at follow-up appointments):

- For 3beta-HSD and 5beta-reductase:
 - Plasma bile acids
 - Urinary bile acids
 - Liver function tests
 - Prothrombin time

- Plasma levels of vitamins A, D and E
- For AMACR
 - Plasma bile acids
 - Urinary bile acids
 - Liver function tests
 - Prothrombin time
 - Plasma levels of vitamins A, D and E
 - Age-appropriate full neuropsychological assessment
- For CYP7A1
 - Total cholesterol
 - Low-density lipoprotein (LDL) cholesterol
 - Liver function tests

AND

Where the product is available cholic acid is used in line with its licensed indication:

- Orphacol has a licence for the “treatment of inborn errors in primary bile acid synthesis due to 3 β -Hydroxy- Δ 5-C27-steroid oxidoreductase deficiency or Δ 4-3-Oxosteroid-5 β -reductase deficiency in infants, children and adolescents aged 1 month to 18 years and adults”.
- Kolbam has a licence for the “treatment of inborn errors in primary bile acid synthesis due to sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α -) methylacyl-CoA racemase (AMACR) deficiency or cholesterol 7 α -hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults”. Please note that Kolbam has not launched officially in the UK ([Specialist Pharmacy Service: Cholic acid](#)), but it does have a European licence and data suggests it has been used in England.

Where the licensed cholic acid product is not available the alternative product can be used off-label provided the Trust undertakes its normal governance processes when prescribing off label medicines.

FOR PEOPLE WITH CTX ONLY: Cholic acid will only be commissioned if treatment with chenodeoxycholic acid is no longer tolerated or effective. Please see above for criteria for commissioning for chenodeoxycholic acid for CTX.

Stopping criteria (cholic acid)

Stop treatment with cholic acid if, after confirming patient compliance with treatment and appropriate dose adjustment, treatment is not effective.

Effectiveness measured using improvement or stabilisation in:

- For CTX:
 - Plasma cholestanol
 - Plasma or urinary bile alcohols
 - Plasma 7 α -hydroxy-cholest-4-en-3-one
 - Clinical features of disease (will vary depending on disease manifestation in individual patients, but appropriate measures include liver disease, diarrhoea, growth, xanthomata, ataxia, neuropathy, and psychiatric and neurological outcomes)
- For 3 β -HSD, 5 β -reductase, AMACR:
 - Plasma bile acids AND/OR urinary bile acids AND
 - Clinical features of disease (will vary depending on disease manifestation in individual patients, but appropriate measures include liver disease, cholestasis and fat-soluble vitamin malabsorption)
- For CYP7A1
 - Total cholesterol AND/OR LDL cholesterol, AND
 - Clinical features of disease.

OR

If there are adverse effects of treatment:

- ADJUST DOSE if
 - Clinically significant deterioration in liver function assessed by:
 - Elevation of serum gamma glutamyltransferase (GGT), alanine aminotransferase (ALT) and/or marked elevation of serum bile acids above baseline levels

- Prolongation of prothrombin time
- STOP TREATMENT if there are worsening in the above tests despite dose adjustment.

Effectiveness and safety measures should be monitored 3-monthly during the first year, 6-monthly during the subsequent 3 years and annually thereafter. Additional or more frequent investigations should be undertaken to monitor therapy during periods of fast growth, concomitant disease and pregnancy, or if there are deranged liver tests.

Cholic acid in combination with chenodeoxycholic acid

The combination of cholic acid and chenodeoxycholic acid is off label. It is proposed to routinely commission the combination:

- in patients who are not responding to monotherapy following 6 months treatment and continue to have biochemical evidence or other disease symptoms as described above suggesting disease progression providing:
 - in the case of CTX a course of cholic acid monotherapy has been undertaken prior to considering dual therapy
 - the patient has no ongoing adverse events to either cholic acid or chenodeoxycholic acid

Stopping criteria (cholic acid and chenodeoxycholic acid in combination)

Stop treatment with the combination of cholic acid and chenodeoxycholic acid if, after confirming patient compliance with treatment and appropriate dose adjustment, treatment is not effective. Effectiveness measured using improvement or stabilisation in:

- Plasma cholestanol
- Plasma or urinary bile alcohols
- Plasma 7 α -hydroxy-cholest-4-en-3-one
- Clinical features of disease (will vary depending on disease manifestation in individual patients, but appropriate measures include liver disease, diarrhoea, growth, ataxia, neuropathy, neurological imaging and psychiatric and neurological outcomes)

9 Proposed Patient Pathway

Specialised inherited metabolic disorder (IMD) centres and centres that specialise in treating liver disease should be responsible for prescribing cholic acid and chenodeoxycholic acid, monitoring and follow-up of patients. Treatment decisions must be initiated, and monitored, by physicians experienced in the management of CTX or inborn errors of primary bile acid synthesis.

10 Proposed Governance Arrangements

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 Teams.

12 Proposed Audit Requirements

NHS England will audit the patient activity through the prior approval system in conjunction with the local teams.

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 chenodeoxycholic acid and cholic acid and the EPARs.

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 not for routine commissioning.

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