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Clinical evidence review of cholic acid for treating inborn errors of primary bile acid synthesis

NHS England unique reference number URN1623 / NICE ID004

Prepared by: NICE on behalf of NHS England Specialised Commissioning

About this clinical evidence review

Clinical evidence reviews are a summary of the best available evidence for a single technology within a licensed indication, for commissioning by NHS England. The clinical evidence review supports NHS England in producing clinical policies but is **not NICE guidance or advice**.

Summary

This evidence review considers cholic acid (Laboratoires CTRS [Orphacol] and Retrophin Europe Ltd [Kolbam]) for treating inborn errors of primary bile acid

synthesis caused by the following enzyme deficiencies in people aged 1 month and over:

- 3-beta-hydroxy-delta5-C27-steroid oxidoreductase (3beta-HSD)
- delta4-3-oxosteroid-5-beta reductase (5beta-reductase)
- 2- (or alpha-) methylacyl-CoA racemase (AMACR)
- sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis [CTX])
- cholesterol 7alpha-hydroxylase (CYP7A1).

Inborn errors of primary bile acid synthesis are rare genetic conditions in which enzyme deficiencies prevent the liver from converting cholesterol in the body to bile acids (such as cholic acid and chenodeoxycholic acid). This results in the liver producing high concentrations of atypical (or 'unusual') bile acids and intermediary metabolites (some of which are toxic to the liver) in an attempt to establish a normal bile acid pool. Accumulation of potentially toxic atypical bile acids and metabolites, and reduced flow of bile acids may cause liver injury. Liver disease associated with these conditions is progressive and if untreated may lead to death from cirrhosis and liver failure. In some cases, this may cause damage to the central nervous system. Clinical features associated with inborn errors of primary bile acid synthesis vary depending on the type of single enzyme deficiency.

Epidemiologic data for each type of single enzyme deficiency are limited. The European public assessment report [EPAR] for Kolbam states the prevalence of people with inborn errors of primary bile acid synthesis in the European Union is 0.07 per 10,000 people. Applied to the population in England, this is approximately 387 people.

The evidence review includes 4 small, prospective observational studies (3 published and 1 unpublished), 3 of which were considered by the European Medicines Agency during the regulatory process for cholic acid replacement therapy (see the European public assessment reports for Orphacol and Kolbam). Some studies included people with peroxisomal disorders, in addition to people with single enzyme deficiency. Smaller studies that were included in the literature review in the

EPARs were summarised and included in the clinical evidence review to supplement the 4 included studies.

Effectiveness

There are 2 proprietary versions of cholic acid, Orphacol and Kolbam, which have different licensed indications, but contain the same active product. The evidence for cholic acid as a whole has been presented, unless otherwise specified.

Atypical urinary bile acid levels are higher than normal in people with inborn errors of primary bile acid synthesis. In the main study by Heubi et al. 2017 (n=54 with single enzyme deficiency, studied over an 18-year period), 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). 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 reduction in the amount of atypical bile acids in the urine suggests that replacement treatment with cholic acid may restore the normal production of bile acids.

Atypical bile acids 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. 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 also supported by 3 other studies and by the literature review reported in the EPARs for cholic acid (Orphacol and Kolbam).

Reduced bile flow in people with inborn errors of primary bile acid synthesis reduces the absorption of fat and fat-soluble vitamins which can affect growth. Height and weight were both reported to have increased after treatment with cholic acid in 3 studies. The main study showed a statistical significant increase in weight only.

People with inborn errors of primary bile acid synthesis may experience certain symptoms (or 'features') commonly associated with the condition. Clinical features such as hepatomegaly (enlargement of the liver), steatorrhoea (fatty stools) and

areflexia (absence of tendon reflexes) were reported to have clinically improved after treatment with cholic acid in 1 study (n=15, median follow-up with treatment 12.4 years). There was a statistically significant improvement in the number of people with steatorrhoea during cholic acid treatment. Another small study (n=15, median follow-up 4.5 years) reported an improvement in clinical features during cholic acid treatment, however the statistical significance of clinical improvement was not reported.

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. One study reporting this outcome found that the number of people with cholestasis and liver dysfunction improved after starting cholic acid 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.

In summary, the studies suggest that replacement therapy with cholic acid may normalise the results of laboratory tests such as liver transaminases and urinary atypical bile acid metabolites, may improve growth and clinical features associated with the condition and may postpone the need for a liver transplant. When interpreting these results, the evidence gaps and limitations (see below) should also be taken into account.

Safety and tolerability

Results from the studies showed that the adverse effects of cholic acid were generally mild-to-moderate in severity, and did not interfere with the therapy. See the summary of product characteristics for Kolbam and Orphacol for further information.

In the main study, there were 3 treatment-related adverse events. These were malaise and jaundice in 1 person and skin lesions in another person, which were thought not to be serious. In the continuation study of the main study, 2 adverse events were considered to be related to cholic acid treatment. These were peripheral

neuropathy in 1 person and nausea in another person, both reported to be of a mild nature that resolved.

The number of people who stopped taking cholic acid treatment was 3 out of 50 in the main study and 4 in the continuation study (total number of people in the safety population was not clearly reported). 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 out of 50 in the main study due to either end-stage liver disease or worsening liver disease. In the continuation study, 3 people died because of either disease progression or thrombosis. In another study, 4 out of 15 people died due to either liver failure, severe cardiomyopathy or complications related to multi-organ primary disease. None of the adverse events leading to death was thought to be related to cholic acid treatment.

Evidence gaps and limitations

There have been no controlled clinical studies of cholic acid for treating inborn errors of primary bile acid synthesis and the rarity of the condition makes such studies unfeasible. The studies included in the evidence review are small, uncontrolled, observational studies and their results should be interpreted with caution. Data were missing for some outcomes. Also, some outcomes were reported as improved, but this was not defined. Many people received additional treatments such as ursodeoxycholic acid as well as cholic acid, which may disguise the true treatment effect of cholic acid. The weaknesses in the studies' design and conduct mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions.

There is no experience of cholic acid treatment for the condition in the elderly population. No data are available for people with renal or hepatic impairment (unrelated to the primary disease). There is limited data on using cholic acid in pregnant women.

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 Orphacol (which is licensed in 3beta-HSD and 5beta-reductase deficiencies) states that the use of cholic acid to treat these conditions has been well established and documented in the literature over a period of almost 20 years. 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.

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Abbreviations

Term	Definition
3beta-HSD	3-beta-hydroxy delta5 C27 steroid oxidoreductase
5beta-reductase	delta4 3- oxosteroid 5 beta reductase
AMACR	2- (or alpha-) methylacyl-CoA racemase
CYP7A1	cholesterol 7alpha-hydroxylase
BAS or BASDs	Bile acid synthesis or bile acid synthesis disorders
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CTX	Cerebrotendinous xanthomatosis (a rare genetic disorder in which an enzyme deficiency prevents cholesterol from being converted to chenodeoxycholic acid
EPAR	European public assessment report (which explains how a medicine, such as cholic acid, was assessed for a license in the EU, and how it may be used)
ULN	Upper level of normal

Medical definitions

Term	Definition
Areflexia	Absence of tendon reflexes
Ataxia	Loss of control of bodily movements
Autosomal recessive inheritance	2 genes that have mutated are inherited, with 1 coming from each parent, causing a genetic disorder
Bile	Fluid produced by the liver that helps to digest fats
Bile acids	Acids in the bile fluid (primarily 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 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
Hepatomegaly	Liver enlargement
Icteric	Yellow discoloration of the skin, see also Jaundice
Inborn errors of primary bile acid synthesis	Rare genetic disorders that lead to deficiencies in enzymes that are needed to 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

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.
Steatorrhoea	Fatty stools
Zellweger spectrum disorders	Type of peroxisomal disorder

1 Introduction

Disease background

1.1 Inborn errors of primary bile acid synthesis are a group of diseases in which the liver does not produce enough primary bile acids due to enzyme deficiencies (British National Formulary for Children). 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).

1.2 Bile acids are made by the liver from cholesterol through a complex series of reactions involving at least 14 enzymatic steps. Failures in these reactions stops bile acid production, which results in a failure to make normal bile acids and, instead, results in the build-up of unusual bile acids and intermediary metabolites (some of which are toxic to the liver). Failure to make bile acids causes reduced bile flow and reduces the absorption of fat and fat-soluble vitamins (Heubi et al. 2007). Identified types of inborn errors of bile acid synthesis include (but are not limited) to:

- 3-beta-hydroxy-delta5-C27-steroid oxidoreductase deficiency (also called 3beta-HSD deficiency or BAS [bile acid synthesis] defect type 1). People with this deficiency develop cholestasis (interruption or suppression of the flow of bile from the liver) and fat-soluble vitamin malabsorption (and various abnormalities secondary to vitamin deficiency) during infancy. If untreated, progressive liver disease occurs (National Organization for Rare Disorders: Bile acid synthesis disorders).
- Delta4-3-oxosteroid 5-beta reductase deficiency (also called 5beta-reductase deficiency or BAS defect type 2). This deficiency presents in a similar way to 3beta-HSD deficiency, but is more severe and, if untreated, can rapidly progress to cirrhosis (normal tissue replaced by scar tissue in the liver) and liver failure (National Organization for Rare Disorders: Bile acid synthesis disorders).

- 2- (or alpha-) methylacyl-CoA racemase deficiency (also called AMACR or BAS defect type 4). People with AMACR deficiency may present with sensory motor neuropathy which causes abnormal sensations, such as numbness or a feeling of pins and needles in the arms and legs, weakness of the muscles, and problems with balance and coordination. Adults with this disorder may lack symptoms until sensory motor neuropathy develops or they may have mild liver disease during childhood. This disorder has also been reported in infants who present with severe fat and fat-soluble vitamin deficiencies and mild cholestasis (National Organization for Rare Disorders: Bile acid synthesis disorders).
- Sterol 27-hydroxylase deficiency (also called cerebrotendinous xanthomatosis [CTX]). This deficiency in sterol 27-hydroxylase causes an accumulation of cholestanol (a derivative of cholesterol) deposits in nerve cells and membranes. This potentially causes damage to the brain, spinal cord, tendons, lens of the eyes and arteries. People with this deficiency may develop cataracts during childhood and benign, fatty tumours (xanthomas) of the tendons during adolescence. If untreated, progressive neurological problems develop in adulthood potentially causing paralysis, ataxia, and dementia. Coronary heart disease is also common (National Organization for Rare Disorders: Bile acid synthesis disorders).
- Cholesterol 7alpha-hydroxylase deficiency (CYP7A1 deficiency). People with CYP7A1 deficiency develop elevated levels of total and low-density lipoproteins, premature gallstones, and premature coronary and peripheral vascular disease. Liver disease is usually absent in this disorder (National Organization for Rare Disorders: Bile acid synthesis disorders).

1.3 The most common inborn errors of primary bile acid synthesis are 3beta-HSD deficiency and 5beta-reductase deficiency, in which primary acid synthesis is absent or negligible (Heubi et al. 2017).

1.4 People with inborn errors of bile acid synthesis may present with cholestasis, fat-soluble vitamin malabsorption and liver disease. Additional symptoms such as progressive neurological disease may develop and can occur in the absence of liver disease. People may also have complications such as rickets, susceptibility to bleeding (bleeding diathesis), night blindness (nyctalopia) and neuroaxonal dystrophy (a progressive 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 (National Organization for Rare Disorders: Bile acid synthesis disorders).

1.5 The age of onset, specific symptoms, and rate of progression can vary greatly from 1 person to another depending on the specific underlying defect. Symptoms are often present at birth or during infancy. However, milder forms of bile acid synthesis disorders with later onset during adulthood have been reported (National Organization for Rare Disorders: Bile acid synthesis disorders).

1.6 Many bile acid synthesis disorders are treated by replacing the missing bile acids (bile acid replacement therapy) (National Organization for Rare Disorders: Bile acid synthesis disorders).

Focus of review

1.7 In line with the marketing authorisation, the focus of this review is cholic acid. There are 2 proprietary versions of cholic acid, which have different indications, but contain the same active ingredient. Therefore, the evidence for cholic acid as a whole is considered in this review, unless otherwise stated. The 2 proprietary versions are:

- Orphacol, which is indicated for treating inborn errors in primary bile acid synthesis in infants, children and young people aged 1 month to 18 years and adults due to the following enzyme deficiencies:
  - 3beta-HSD

- 5beta-reductase.

- Kolbam, which is indicated for treating inborn errors in primary bile acid synthesis in infants, children and young people aged 1 month to 18 years and adults due to the following enzyme deficiencies:
  - sterol 27-hydroxylase (presenting as CTX)
  - AMACR
  - CYP7A1.

Epidemiology and needs assessment

1.8 Epidemiologic data for each type of single enzyme deficiency are limited. The European public assessment report [EPAR] for Kolbam states the prevalence of people with inborn errors of primary bile acid synthesis in the European Union is 0.07 per 10,000 people. Applied to the population in England, this is approximately 387 people.

1.9 The summary of product characteristics for Orphacol states in Europe there are about 3 to 5 people with 3beta-HSD deficiency per 10 million people, and an estimated ten-fold lower prevalence for 5beta-reductase deficiency.

1.10 Fewer than 10 cases of people with AMACR deficiency have been reported in the medical literature (National Organization for Rare Disorders: Bile acid synthesis disorders).

1.11 A bibliographic study of the epidemiology and prevalence of rare diseases in Europe estimated that there are about 200 people with sterol 27-hydroxylase deficiency (CTX) and worldwide there are 24 cases of CYP7A1 deficiency (EURODIS and ORPHANET: Rare diseases in numbers and the prevalence of rare diseases).

Product overview

Mode of action

1.12 Cholic acid is one of the main primary bile acids produced by the liver. Cholic acid treatment replaces the missing cholic acid in people with

inborn errors of primary bile acid synthesis. Treatment restores the bile acid-dependent component of bile flow, restoring biliary secretion and biliary elimination of toxic metabolites. It inhibits the production of toxic bile acid metabolites by negative feedback on cholesterol 7alpha-hydroxylase, which is the rate-limiting enzyme in bile acid synthesis, and improves nutritional status by correcting intestinal malabsorption of fats and fat-soluble vitamins (EPAR: Orphacol and Kolbam and summary of product characteristics: Orphacol).

Regulatory status

1.13 Orphacol received a marketing authorisation in September 2013 for treating inborn errors in primary bile acid synthesis due to 3beta-HSD deficiency or 5beta-reductase deficiency in infants, children and young people aged 1 month to 18 years and adults.

1.14 Kolbam received a marketing authorisation in November 2015 for treating inborn errors in primary bile acid synthesis due to sterol 27-hydroxylase (CTX) deficiency, AMACR deficiency or CYP7A1 deficiency in infants, children and young people aged 1 month to 18 years and adults.

Dosing information

1.15 Orphacol is available as 50 mg and 250 mg capsules for oral administration. The daily dose ranges from 5 to 15 mg/kg in infants, children, young people and adults. In all age groups, the minimum dose is 50 mg. The dose is adjusted in 50 mg steps, and the daily dose can be divided. In adults, the daily dose should not exceed 500 mg (summary of product characteristics: Orphacol).

1.16 Kolbam is also available as 50 mg and 250 mg capsules for oral administration. The recommended daily dose is 10 to 15 mg/kg either as a single daily dose or in divided doses, for both adults and children. The dose can be subsequently titrated, not exceeding a maximum of 15 mg/kg/day (summary of product characteristics: Kolbam).

1.17 Cholic acid treatment should be initiated and monitored by specialists experienced in the management of the specific deficiencies. During initiation of treatment and dose adjustment, serum and/or urine bile acid levels should be monitored intensively (at least every 3 months during the first year of treatment and every 6 months during the second year). The concentrations of abnormal bile acid metabolites should be determined and, at each investigation, the need for dose adjustment considered. The lowest dose of cholic acid that effectively reduces bile acid metabolites to as close to zero as possible should be chosen (summary of product characteristics: Orphacol and Kolbam).

Treatment pathway and current practice

1.18 There are no published, agreed, UK-based treatment pathways for treating inborn errors of primary bile acid synthesis. Orphacol and Kolbam received marketing authorisations for treating inborn errors of primary bile acid synthesis in 2013 and 2015 respectively, for non-overlapping subtypes of inborn errors of primary bile acid synthesis. However, cholic acid has been used off-label in England for around 20 years for this indication.

1.19 The Orphanet (a European consortium of 40 countries, including the UK, that gathers information on rare diseases) monographs for 3beta-HSD deficiency (BAS defect type 1), 5beta-reductase deficiency (BAS defect type 2) and AMACR deficiency (BAS defect type 4) state that first-line treatment is cholic acid. Clinical experts who commented on this evidence review suggest that in the UK, people with 3beta-HSD deficiency are also treated with combination of cholic acid and chenodeoxycholic acid and that this combination treatment has been reported in a study by Subramaniam et al. 2010. For the treatment of 5beta-reductase deficiency, ursodeoxycholic acid may be used but is not considered the treatment of choice because it does not suppress atypical bile acid synthesis and the toxic metabolites that may injure the liver continue to be produced (Orphanet monograph for AMACR deficiency).

1.20 The Orphanet monograph for cerebrotendinous xanthomatosis (sterol 27-hydroxylase deficiency) states that first-line treatment is chenodeoxycholic acid, which normalises bile acid synthesis and cholestanol concentrations. Statins may also be used alone or in combination with chenodeoxycholic acid. Cholic acid has been used as an alternative to chenodeoxycholic acid. The Orphanet monograph states that cholic acid is not as effective for suppressing bile acid synthesis and the production of cholestanol, but it lacks lack the potential toxic effects on the liver sometimes associated with chenodeoxycholic acid. However, no evidence to support this statement is provided.

1.21 No treatment pathway information was found for CYP7A1 deficiency.

1.22 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.

2 Evidence

Literature search

2.1 A literature search was done, which identified 710 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and 23 full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and 3 published studies were included in the clinical evidence review. One unpublished study from the European public assessment report (EPAR) for Kolbam was also included (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons).

Overview of included studies

2.2 There are 2 proprietary versions of cholic acid (Orphacol and Kolbam), which have different indications, but contain the same active ingredient.

Therefore the evidence for cholic acid as a whole has been presented, unless otherwise specified.

2.3 One phase 3, open-label, single-arm, non-randomised, non-comparative compassionate treatment study (Heubi et al 2017, study CAC-91-10-10, the main study) conducted over 18 years and 2 prospective observational studies,Al-Hussaini et al 2017 (follow-up of 10 years) and Gonzales et al. 2009 (median follow-up of 12.4 years were identified from the search and included in this evidence review. An additional 33-month phase 3, open-label, single-arm, non-randomised, non-comparative study (study CAC-002-001), which was considered by the European Medicines Agency during the regulatory process, was also included. This study was unpublished at the time of the search. A summary of the characteristics of the included studies is shown in table 1 (see evidence tables for details).

2.4 Literature reviews included in the EPARs for Orphacol and Kolbam were also used as part of the evidence review. Both EPARs reported data from Gonzales et al. 2009. Most of these studies reported in the literature review were identified in the literature searches, however these were excluded because they did not meet the inclusion criteria, mainly because the intervention was not cholic acid monotherapy, studies included less than 14 people and some were reported in review papers. Smaller studies in the EPAR's literature review that reported treatment with cholic acid monotherapy were summarised and included in the evidence review to supplement the included studies. Data from the literature reviews were not assessed for quality.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Heubi et al. 2017 (study CAC-91-10-10)	Children with BASD due to single enzyme defects (n=54)[a] or peroxisomal disorders (n=31) n=85 in total	Intervention: oral cholic acid 10 to 15 mg/kg daily No comparator	Changes from worst pre-to best post-treatment in: • Atypical urinary bile acids • Liver chemistries

			• Height and weight
Gonzales et al. 2009	Children with 3beta-HSD deficiency or 5beta-reductase deficiency n=15[b]	Intervention: oral cholic acid mean dose 13 mg/kg daily initially No comparator	Not stated. The study reports results of physical examination, laboratory results, sonography, urine analysis and liver biopsies during cholic acid treatment
Al-Hussaini et al. 2017	Children with BASD[c] n=15	Intervention: oral cholic acid 10 to 15 mg/kg daily No comparator	Response to cholic acid treatment which was defined as complete resolution of cholestasis and/or liver dysfunction and survival with native liver
CAC-002-001[d]	Children with BASD due to single enzyme defects (n=29)[e] or peroxisomal disorder (n=12) n=41in total	Intervention: oral cholic acid 10 to 15 mg/kg daily No comparator	Changes in baseline to the worst post-baseline response in: • Urine bile acids • Transaminases • Bilirubin • Height and weight percentiles

[a] Intention to treat population, 3beta-HSD deficiency (n=35), 5beta-reductase deficiency (n=10), sterol 27-hydroxylase deficiency (CTX) (n=5), AMACR deficiency (n=1), others (n=2), unknown (n=1).

[b] 3beta HSD deficiency (n=13), 5beta-reductase deficiency (n=2)

[c] 3beta HSD deficiency (n=11), 5beta-reductase deficiency (n=3)

[d] This study was a continuation study of studies CAC-91-10-10 and CAC-001-01 that also recruited newly diagnosed patients who were treatment naïve

[e] 3beta HSD deficiency (n=21), 5beta-reductase deficiency (n=4), Sterol 27-hydroxylase deficiency (CTX) (n=4)

Abbreviations: 3beta-HSD, 3-beta-hydroxy-delta5-C27-steroid oxidoreductase; 5beta-reductase, delta4-3-oxosteroid-5-beta reductase; AMACR, 2- (or alpha-) methylacyl-CoA racemase; BASD, bile acid synthesis disorders

Key outcomes

2.5 The key outcomes identified in the scope are discussed below for effectiveness and safety. Table 2 below provides a grade of evidence summary of key outcomes (see appendix 5 for the details of grading evidence). The more detailed evidence tables and results for each study are in appendices 3 and 4.

2.6 **Grade of evidence:** the grade of evidence for the majority of the outcomes is B because (apart from response to cholic acid treatment, which was based on 1 study and graded C) the evidence is based on more than 1 study scoring 4–6 points, which are directly applicable to people with the indication of interest (apart from study CAC-002-001 which was indirectly applicable as it also included people with peroxisomal disorders and reported combined results).

2.7 **Limitations:** key limitations include the small numbers of people in the studies (in particular people with sterol 27-hydroxylase, AMACR and CYP7A1 deficiencies), their observational study designs and the lack of comparators. Data were inadequately reported for all people for some outcomes, and confounded by time and by concomitant treatment with ursodeoxycholic acid (in some people) and patient management. Few statistical analyses were undertaken. Some outcomes reporting 'improvement' were not clearly defined in the studies.

Effectiveness

Atypical urinary bile acids

2.8 People with inborn errors of primary bile acid synthesis produce atypical (or 'unusual') bile acids which are eliminated in the urine and can be measured to confirm the diagnosis of the enzyme deficiency and examine the effect of cholic acid. Treatment with bile acids, such as cholic acid, aims to reduce levels.

2.9 A reduction in atypical urinary bile acids was reported in all studies. Heubi et al. 2017 compared worst pre-treatment urine bile acid scores with best post-treatment scores. There was a statistically significant decrease in the percentage of people (single enzyme deficiencies, n=43 in the modified intention to treat population [MITT] with marked abnormalities in atypical bile acid score after treatment with cholic acid (72.1% pre-treatment compared with 14% post-treatment, $p<0.0001$, modified intention to treat population [MITT]). The EPAR for Kolbam reported the results of this outcome by the different types of bile acid synthesis disorders. In the

worst pre-treatment to best post-treatment analysis, there was a decrease in the percentage of people with 3beta-HSD (n=32) with marked abnormalities in atypical urinary bile acid score, however it was not clear whether this finding was statistically significant. Improvements for this outcome were seen in the small number of people with 5beta-reducatse deficiency (n=6), sterol 27-hydroxylase (n=3) and AMACR deficiency (n=1), however the improvements were not statistically significant.

2.10 In the continuation study CAC-002-001 (single enzyme deficiencies, n=29), similar analysis found a non-statistical significant decrease in the percentage of patients with marked or significant elevation in atypical bile acids (numerical data not available). Gonzales et al. 2009 found that cholic acid treatment was associated with a statistically significant decrease in atypical urinary bile acids from baseline to all time points in the study ($p<0.005$ at 5 years and at last visit [varied between patients] in people with 3beta-HSD deficiency [n=13]). A decrease in atypical urinary bile acids from baseline to all time points was also shown in people with 5beta-reducatse deficiency (n=2), however statistical significance was not reported. Al-Hussaini et al. 2017 reported a “marked” reduction in atypical urinary bile acids metabolites after starting cholic acid which was concomitant with improvement of cholestasis (statistical analysis was not reported).

2.11 Data from the literature review in the EPARs for cholic acid showed similar results. The EPAR for Orphacol stated there was a significant decrease in atypical bile acids and of total urinary bile acid excretion, indicating an improvement of cholestasis. One study described disappearance of atypical bile acids from urine within 1 week of treatment with cholic acid for 25 people with 3beta-HSD deficiency (EPAR: Orphacol). One study reporting 2 siblings in the literature review found that changing treatment from ursodeoxycholic acid to cholic acid in the male sibling aged 14 months with CTX resulted in a good biochemical response and a marked reduction in bile alcohol excretion and he was reported to have remained “clinically normal” at 8 years of age. The

younger female sibling with CTX started treatment with cholic acid at age 5 months. She did not develop jaundice or abnormal liver function and remained free of liver symptoms at 7 years of age, however there was some evidence that neurodevelopment may have been slightly below average (EPAR: Kolbam).

Liver function

2.12 Liver function tests such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are used to examine how well the liver is functioning. People with inborn errors of primary bile acid synthesis disorders produce unusual bile acids that can be toxic to the liver. This can cause liver disease and if untreated, may lead to death from cirrhosis and liver failure. Treatment with cholic acid aims to replace the missing bile acid to stop the production of toxic bile acids.

2.13 Liver function test results were generally reported to be improved after treatment with cholic acid in all studies. Heubi et al. 2017 found a statistically significant improvement in ALT and AST levels from baseline to after treatment with cholic acid ($p<0.0001$, worst to best analysis) in people with single enzyme deficiencies. In people with 3beta-HSD, 5beta-reductase, sterol 27-hydroxylase and AMACR deficiencies, the ALT and AST levels improved after treatment with cholic acid, with more people reporting levels to be below the upper level of normal. In the best pre-treatment to best post-treatment analysis, LFT changes for people with 3beta-HSD deficiency were reported to be statistically significant.

2.14 In the continuation study, CAC-002-001, no statistically significant changes were reported from baseline to worst post-treatment analysis. However, the AST levels from baseline to best post -treatment, showed a statistical significant improvement ($p<0.05$). Gonzales et al. 2009 reported that total serum bilirubin concentrations and serum ALT levels were abnormal at the beginning of the study in 12 and 11 people, respectively. However after treatment with cholic acid, these liver function test results

were normalised in all people and remained normal at follow-up (at 5 years and at last visit; p<0.0001). In the study by Al-Hussani et al. 2017, 11 out of 15 people taking cholic acid had normal liver chemistries after a median follow-up period of 4.5 years (range 1 to 11.5 years).

2.15 In the study by Gonzales et al. 2009, at baseline, liver samples showed that 12 out of 13 people with 3beta-HSD deficiency had severe cholestasis. After treatment with cholic acid (mean follow-up 6.2 years), cholestasis was reported to be resolved in all 12 people.

2.16 According to the literature review in the EPAR for Orphacol, liver function tests were consistently reported as improved on treatments containing cholic acid in people with 3beta-HSD and 5beta-reductase deficiencies. Liver transaminases such as ALT and AST, total bilirubin and direct bilirubin were consistently reported as decreasing with cholic acid treatment. In 1 study, liver enzymes were reported to be in their normal range within 10 months of cholic acid and ursodeoxycholic acid combination therapy, and remained stable following cholic acid monotherapy for a mean period of 4.2 years (EPAR: Kolbam).

2.17 Liver histology was not clearly reported in the 4 studies included for the evidence review. The EPAR for Orphacol states that although there was data for liver histology before starting bile acid treatment in some of the studies, follow-up data were limited to a small number of people with 3beta-HSD and 5beta-reductase deficiencies. Where data were available in the literature review, a resolved liver pathology was found in some and fibrosis (mild or septal) remained in others during treatment with cholic acid.

Height and weight

2.18 Inborn errors of primary bile acid synthesis affects the absorption of fat and fat-soluble vitamins in the intestines, which can affect growth. Treatment with cholic acid aims to replace the missing bile acid needed to facilitate the absorption of fat and fat-soluble vitamins.

2.19 Heubi et al. 2017 found that height and weight percentiles increased from the worst pre-treatment value to the best post-treatment value in people with single enzyme deficiencies (MITT analysis). However, statistical significance was reported only for the change in weight (p=0.006). A non-statistically significant increase in mean height and weight percentiles was seen in each type of single enzyme deficiency in the worst pre-treatment to best post-treatment analysis, mainly in people with 3beta-HSD, sterol 27-hydroxylase and AMACR deficiencies. However, only an increase in mean weight percentile was seen in people with 5beta-reductase deficiency (EPAR: Kolbam).

2.20 Similar increases were shown in study CAC-002-001, but these changes were not statistically significant. In the study by Gonzales et al. 2009, growth in weight and height improved from means of −0.25 SD and −0.50 SD, respectively, up to a mean of +1 SD for both.

2.21 Vitamin malabsorption was not clearly reported in the included studies. The EPAR for Orphacol states that the levels of serum vitamin E remained normal with cholic acid treatment after vitamin E supplements were stopped in the study by Gonzales et al. 2009.

Clinical features

2.22 People with inborn errors of primary bile acid synthesis may present with particular symptoms such as cholestasis, steatorrhoea (fatty stools) or hepatomegaly (enlargement of the liver), but these differ depending on the enzyme deficiency. Treatment with cholic acid aims to reduce symptoms associated with the condition.

2.23 All people were reported to have hepatomegaly at baseline (n=15) in the study by Gonzales et al. 2009. After 5 years and at last visit, the number of people with hepatomegaly reduced to 4 and 1 respectively. Steatorrhoea was reported to resolve at 5 years of cholic acid treatment in 9/13 people who had it at baseline (p<0.005). Areflexia (absence of tendon reflexes) was reported to be present in 7 people at baseline. At 5 years and at last visit after cholic acid treatment, the number of people

with areflexia reduced to 3 and 4 people respectively. Al-Hussaini et al. 2017 found that the clinical condition in 12/15 people treated with cholic acid had clinically improved. Splenomegaly (enlargement of the spleen) and hepatomegaly were reported to resolve slowly after starting treatment with cholic acid, taking several months or years to clinically improve (numerical data not provided).

Response to cholic acid treatment

2.24 People with inborn errors of primary bile acid synthesis accumulate toxic substances because of reduced flow of bile acid and this can cause liver injury. This can result in cholestasis, the liver not functioning as it should do (liver dysfunction) and progressive liver disease. If untreated this may lead to needing a liver transplant or death from cirrhosis and liver failure. This outcome is a measure of how long after starting cholic acid treatment people with the condition are expected to see improvement in cholestasis and liver dysfunction and also how many people survived without the need for a liver transplant.

2.25 Out of 15 people in the study by Al-Hussaini et al. 2017, 11 were reported to survive after a median follow-up period of 4.5 years (range 1 to 11.5 years). Ten of these had their native liver and 1 had a liver transplant 2 months after starting treatment with cholic acid. Cholestasis was reported to improve, but no numerical data were given. Liver dysfunction was not clearly reported in the study.

2.26 The literature review in the EPAR for Orphacol included 21 people with 3beta-HSD deficiency treated with cholic acid. Of the 21 people, 1 person with significant pre-existing liver damage was reported to need a liver transplant, 7 people were reported to have a “generally favourable” outcome, 5 people were reported to survive more than 12 years without complications, and the remaining people were reported to need additional care. Reports of 10 older, untreated siblings of these people showed that their untreated siblings died as children before a definite diagnosis of the condition or before treatment could be established, One person was

reported to have survived without treatment to the age of 26 years, at which time they needed treatment. The EPAR for Orphacol states that these survival data are supported by biochemical and histological data.

2.27 The EPAR for Orphacol which is licensed for 3beta-HSD and 5beta-reductase deficiencies states that the use of cholic acid to treat these conditions has been well established and documented in the literature over a period of almost 20 years. It states that all children diagnosed with 3beta-HSD deficiency or 5beta-reductase deficiency have died due to liver failure before the introduction of bile acid therapy, whereas all children that have been treated with cholic acid to date were alive, most had not needed a liver transplant and were in general good health, leading normal lives.

2.28 According to the EPAR for Kolbam, the effectiveness of cholic acid for the treatment of sterol 27 hydroxylase (CTX), AMACR and CYP7A1 deficiencies was based on the results across all single enzyme deficiencies associated with inborn errors of bile acid synthesis included in the studies (this included people with 3beta-HSD and 5beta-reductase deficiencies) and literature data. The EPAR states that for each of the enzyme deficiencies, the therapeutic benefit of cholic acid comes from the same mechanism, namely the ability to inhibit transcription of the 7-alpha hydroxylase. The EPAR also states that whilst the magnitude of changes in metabolic and pathologic parameters may differ in each different phenotype, it is evident that an effective cholic acid preparation will be therapeutically efficacious in each.

Safety and tolerability

2.29 In the study by Heubi et al. 2017, 3 treatment-related adverse events (malaise, jaundice and skin lesions) in 2/50 (4%) people with single enzyme deficiencies were reported (mean duration of treatment 145 weeks). None were considered to be serious in this population. The EPAR for Kolbam states that in study CAC-002-001 there were 2 adverse events considered to be related to cholic acid treatment in 2 people.

These were peripheral neuropathy and nausea, both reported to be of a mild nature that resolved. It was unclear in the EPAR if this was in people with single enzyme deficiencies and/or peroxisomal disorders

2.30 The EPAR for Kolbam states that, during the 33-month study period of CAC-002-001, approximately half the people experienced treatment-emergent adverse events. A decrease in Vitamin D was the most common treatment-emergent adverse event followed by disease progression, an increase in liver enzymes and upper respiratory tract infection in people with single enzyme deficiency and/or peroxisomal disorders.

2.31 Out of the 44 adverse events reported in 21/50 people (42%) in the study by Heubi et al. 2017, 6 were reported to be serious in 5/50 people with single enzyme deficiency (10%). In people with single enzyme deficiency and peroxisomal disorder, disease progression was frequently reported, followed by diarrhoea (3%), urinary tract infection (3%) and dehydration (3%). These results need to be interpreted with caution as a higher percentage of people with peroxisomal disorder reported serious adverse events (22%) compared with people with single enzyme deficiencies. In the study by Gonzales et al. 2009, no serious adverse events were reported in people with a cumulative duration of treatment of more than 180 patient-years. However, cholic acid overdose was reported in 4 people. The clinical features of overdose included pruritis, diarrhoea, and transient increases in serum bile acids, gamma-glutamyltransferase and alanine aminotransferase. Symptoms resolved after reducing the dose of cholic acid.

2.32 Three adverse events leading to discontinuing cholic acid treatment in 3/50 people with single enzyme deficiency (6%) were reported in the study by Heubi et al. 2017. The most common reason for discontinuing treatment was because of disease progression and not thought to be related to cholic acid treatment. In study CAC-002-001, 4 people

discontinued the study due to treatment-emergent adverse events (disease progression in 3 and peripheral neuropathy in 1 person).

2.33 In the study by Heubi et al. 2017, 7 people with single enzyme deficiency died during the cholic acid treatment. Four people with 5beta-reductase deficiency had end-stage liver disease at the time of diagnosis and start of treatment and deteriorated despite therapy, 3 people had worsening liver disease (1 with 3beta-HSD deficiency and 2 with other enzyme deficiencies). In study CAC-002-001, 3 people (1 with single enzyme deficiency and 2 with peroxisomal disorder) died of disease progression and thrombosis. According to the EPAR for Kolbam, none of the adverse events leading to death was considered related to cholic acid in study CAC-002-001. In the study by Al-Hussaini et al. 2017, 4 people died. This included 3 people with single enzyme deficiency. Cause of deaths were liver failure (n=2), severe cardiomyopathy and complications related to multi-organ primary disease.

2.34 The EPARs for Kolbam and Orphacol also include safety data from case reports from the literature, which are generally consistent with the safety profile reported in the studies included in the evidence review. The development of gallstones requiring cholecystectomy has been observed in 1 person with 3beta-HSD deficiency (EPAR: Kolbam). The summary of characteristics includes gallstones as an undesirable effect after long-term treatment with cholic acid.

2.35 According to the EPAR for Kolbam, although the uncontrolled nature of the data made it difficult to evaluate causal association, it was possible to conclude that the adverse events reported with cholic acid in the studies were generally not serious and mostly related to the underlying disease condition.

Evidence gaps and limitations

2.36 There have been no randomised controlled clinical studies of cholic acid in inborn errors of primary bile acid synthesis. The rarity of the condition

makes such studies unfeasible, because it would need to involve many centres and have a long follow-up period. No dose-response studies have been undertaken. The EPAR for Orphacol states that dosing is based on previous clinical experience with patients' response to bile acids including cholic acid.

2.37 The efficacy and safety of cholic acid for inborn errors of primary bile acid synthesis has been studied in 4 prospective observational studies (1 of which was a continuation study of the main study) in single centres in the USA, Europe and Saudi Arabia. The main limitations of the studies include their small size (n=50 or less with single enzyme deficiency), lack of control groups and their open-label nature, which mean they are subject to bias and confounding. The methods used to examine some outcome measures were not clearly reported in the studies. Numerical data and statistical analyses for some of the efficacy outcomes were not clearly reported in the studies. Data were missing for some outcomes and some outcomes were reported as improved, but this was not defined. There may be some uncertainty in using the same outcome measures for all the single enzyme deficiencies because they present with different clinical features. For example, clinical features of people with CTX (see also clinical evidence review of chenodeoxycholic acid) differ to those with 3beta-HSD deficiency. Also, there is some overlap of people with the condition who have been included in more than 1 study. This may lead to double counting of people across the studies.

2.38 Cholic acid treatment was commonly studied in infants from 1 month onwards, children and young people. The average age of the population in the study by Heubi et al. 2017 and Gonzales et al. 2009 was approximately 3 years at the start of cholic acid treatment. According to the summary of product characteristics for Kolbam, in study CAC-002-001 the mean age at baseline was 9 years (range 3 months to 35 years). There is limited data on starting treatment in adults. There is no experience of cholic acid treatment for the condition in the elderly population.

2.39 No data are available for people with renal or hepatic impairment (unrelated to the primary disease) and they should be carefully monitored and the dose titrated individually. There is limited data on using cholic acid in pregnant women. In the study by Gonzales et al. 2009, 4 normal pregnancies were reported in 2 people taking cholic acid. The summary of product characteristics for Kolbam states that the use of cholic acid may be considered during pregnancy if the doctor considers that the benefits to the patient outweigh the possible risk. As a precautionary measure, pregnant women and their unborn children should be closely monitored (summary of product characteristics: Orphacol).

2.40 A total of 112 people with single enzyme deficiency were included in the 4 studies. For 2 of the studies, there was an overlap of same people with the condition as 1 study was a continuation study of the main study. Most people included in the studies had 3beta-HSD deficiency (n=80), followed by 5beta-reductase deficiency (n=19), sterol 27-hydroxylase deficiency (CTX) (n=9), AMACR deficiency (n=1) and others/unknown (n=3). According to the EPAR for Kolbam, 1 person with CYP7A1 deficiency was included in the main study reported by Heubi et al. 2017.

Table 2 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Abnormal urinary bile acids	Heubi et al. 2017	6/10	Directly applicable	B	Bile acids are substances removed from the body in urine. Abnormal urinary bile acid levels are higher than normal in people with inborn errors of primary bile acid synthesis. This outcome compared the average level of abnormal bile acids in people's urine before and after cholic acid to see if treatment reduced the amount. The main study (Heubi et al. 2017, n=54) found a statistically significant reduction in the percentage of people with abnormal urinary bile acids after treatment (14%; compared with before treatment 72.1%; p<0.0001) over an 18-year period. Similar results were shown in supporting studies and the literature review of smaller studies from the EPARs. Results suggest treatment with cholic acid may reduce abnormal urinary bile acids in people with inborn errors of primary bile acid synthesis, indicating a reduction in the production of toxic bile acids that can have an adverse effect on the liver. Results should be interpreted with caution because studies were small, uncontrolled, unblinded and non-comparative. Some people received additional treatment with ursodeoxycholic acid as well as cholic acid, which may disguise the true treatment effect of cholic acid. The design and conduct of the studies mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions. Cholic acid is licensed for 5 different subtypes of inborn error of bile acid synthesis, but results were not generally reported by subtype, and the subtypes had uneven representation across and within studies.
	Study CAC-002-001	6/10	Indirectly applicable		
	Gonzales et al. 2009	6/10	Directly applicable		
	Al-Hussaini et al. 2017	5/10	Directly applicable		
Liver function	Heubi et al. 2017	6/10	Directly applicable	B	ALT and AST levels are used to assess 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. This outcome compared levels of liver enzymes in blood before and after treatment to see if liver function improved. The main study (Heubi et al. 2017, n=54) found statistically significant improvements in ALT and AST after treatment compared with before treatment (p<0.0001). In the continuation study, AST values were reported to have a statistical significant improvement from before treatment to the best value after treatment (p<0.005). Improvement in liver function was also supported by Gonzales et al. 2009 and Al-Hussaini et al. 2017. Data from the literature review consistently showed liver function tests as being improved on treatments containing cholic acid
	Study CAC-002-001	6/10	Indirectly applicable		
	Gonzales et al. 2009	6/10	Directly applicable		
	Al-Hussaini	5/10	Directly applicable		

	et al. 2017				in people with 3beta-HSD and 5beta-reductase deficiencies. Results suggest treatment with cholic acid may improve liver function in people with inborn errors of primary bile acid synthesis. Results should be interpreted with caution because studies were small, uncontrolled, unblinded and non-comparative. Data were not clearly reported for the outcome and some people received additional treatment with ursodeoxycholic acid, which may disguise the true treatment effect of cholic acid. The design and conduct of the studies mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions. Cholic acid is licensed for 5 different subtypes of inborn error of bile acid synthesis, but results were not generally reported by subtype, and the subtypes had uneven representation across and within studies.
Height and weight	Heubi et al. 2017	6/10	Directly applicable	B	Inborn errors of primary bile acid synthesis affect the absorption of fat and fat-soluble vitamins in the intestines, which can affect growth. This outcome compared height and growth before and after treatment. The main study (Heubi et al. 2017, n=54) found an increase in height and weight percentiles after treatment compared with before treatment. However, statistical significance was reported only for the change in weight (p=0.006). Similar increases in growth were shown in CAC-002-001 and Gonzales et al. 2009 but statistical significance was not reported. Results suggest treatment with cholic acid may help to improve growth in people with inborn errors of primary bile acid synthesis. Results should be interpreted with caution because studies were small, uncontrolled, unblinded and non-comparative. Some people received additional treatment with ursodeoxycholic acid as well as cholic acid, which may disguise the true treatment effect of cholic acid. The design and conduct of the studies mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions. Cholic acid is licensed for 5 different subtypes of inborn error of bile acid synthesis, but results were not generally reported by subtype, and the subtypes had uneven representation across and within studies.
	Study CAC-002-001	6/10	Indirectly applicable		
	Gonzales et al. 2009	6/10	Directly applicable		
Clinical features	Gonzales et al. 2009	6/10	Directly applicable	B	People with inborn errors of primary bile acid synthesis may present with some common symptoms (or clinical features) associated with the condition, such as fatty stools. This outcome compared clinical features before and after treatment. Gonzales et al. 2009 (n=15 people with 3beta-HSD deficiency and 5beta-reductase deficiency) found the number of people with an enlarged liver (hepatomegaly), fatty stools (steatorrhoea, p<0.005) and absent tendon reflexes (areflexia) reduced from
	Al-Hussaini et al.	5/10	Directly applicable		

	2017				15, 13, and 7 people at baseline to 4, 9, and 3 people respectively after 5 years of treatment. Al Hussaini et al. 2017 found the clinical condition in 12/15 people treated with cholic acid had clinically improved. Results suggest treatment with cholic acid may improve some of the clinical features in people with inborn errors of primary bile acid synthesis. Results should be interpreted with caution because studies were small, uncontrolled, unblinded and non-comparative. Data were not clearly reported for the outcome and the term 'improved' was not defined. Statistical significance of the results was not reported. Some people received additional treatment with ursodeoxycholic acid as well as cholic acid, which may disguise the true treatment effect of cholic acid. The design and conduct of the studies mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions. Cholic acid is licensed for 5 different subtypes of inborn error of bile acid synthesis, but results were not generally reported by subtype, and the subtypes had uneven representation across and within studies.
Response to cholic acid treatment	Al-Hussaini et al. 2017	5/10	Directly applicable	C	People with inborn errors of primary bile acid synthesis accumulate toxic substances because of reduced flow of bile acid and this can result in reduced flow of bile from the liver (cholestasis), the liver not functioning as it should do (liver dysfunction), liver failure and death due to disease progression. This outcome is a measure of how long after starting cholic acid treatment people with the condition are expected to see an improvement in cholestasis and liver dysfunction, and also how many people survived with their own liver. Al-Hussaini et al. 2017 found 11/15 people were reported to survive after a median follow-up of 4.5 years; 10 of these had their own liver and 1 had a liver transplant 2 months after starting treatment with cholic acid. Cholestasis was reported to improve, but no numerical data were given. Liver dysfunction was not clearly reported in the study. 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. It is unclear from this study whether treatment with cholic acid affected survival and the need for a liver transplant because there is 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. Results of the study should be interpreted with caution because it was small, uncontrolled, unblinded and non-comparative. Data were not clearly reported for the outcome and some people received additional treatment with ursodeoxycholic acid before cholic acid treatment was started, which may disguise the true treatment

					effect of cholic acid. The design and conduct of the study means it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions. Cholic acid is licensed for 5 different subtypes of inborn error of bile acid synthesis, but results were not generally reported by subtype, and the subtypes had uneven representation across and within studies
Treatment-related adverse events	Heubi et al. 2017	6/10	Directly applicable	B	This outcome looks at how many adverse events related to cholic acid occurred during the study. In the main study by Heubi et al. 2017, 3 adverse events were considered to be related to cholic acid treatment. These were malaise and jaundice in 1 person and skin lesions in another person, which were thought not to be serious. In CAC-002-001, 2 adverse events were considered to be related to cholic acid treatment. These were peripheral neuropathy in 1 person and nausea in another person, both reported to be of a mild nature that resolved. Results suggest that some people who take cholic acid may experience adverse events related to cholic acid treatment. Results should be interpreted with caution because studies were small, uncontrolled, unblinded and non-comparative. Some people received additional treatment with ursodeoxycholic acid as well as cholic acid, which may disguise the true treatment effect of cholic acid. The design and conduct of the studies mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions. Cholic acid is licensed for 5 different subtypes of inborn error of bile acid synthesis, but results were not generally reported by subtype, and the subtypes had uneven representation across and within studies
	Study CAC-002-001	6/10	Indirectly applicable		
Serious adverse events	Heubi et al. 2017	6/10	Directly applicable	B	This outcome looks at how many adverse events occurred during the study, which were considered to be serious, rather than mild or moderate. The main study by Heubi et al. 2017, found 6 serious adverse events in 5 people with single enzyme deficiency. These were disease progression (most frequently reported), diarrhoea (3%), urinary tract infection (3%) and dehydration (3%) which were thought not to be related to cholic acid treatment. The study by Gonzales et al. 2009 reported cholic acid overdose in 4 people that caused pruritis, diarrhoea, and transient increases in serum bile acids, gamma-glutamyltransferase and alanine aminotransferase. These symptoms resolved after reducing the dose of cholic acid. Results suggest that some people with the condition may be at risk of a serious adverse event that is more likely to be related to their condition rather than cholic acid treatment. Results should be interpreted with caution because studies were small,
	Gonzales et la. 2009	6/10	Directly applicable		

					uncontrolled, unblinded and non-comparative. Some people received additional treatment with ursodeoxycholic acid as well as cholic acid, which may disguise the true treatment effect of cholic acid. In addition, the frequencies in serious adverse events reported in the main study included people with peroxisomal disorders as well as single enzyme deficiency disorders. The design and conduct of the studies mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions. Cholic acid is licensed for 5 different subtypes of inborn error of bile acid synthesis, but results were not generally reported by subtype, and the subtypes had uneven representation across and within studies.
Discontinuation of cholic acid treatment	Heubi et al. 2017	6/10	Directly applicable	B	This outcome considered how many people had to stop taking cholic acid during the study. The main study, Heubi et al. 2017, found 3 people stopped taking cholic acid. The most common reason for stopping treatment was because of disease progression and not thought to be related to cholic acid treatment. In CAC-002-001, 4 people stopped taking cholic acid. Three people stopped treatment because of because of disease progression and 1 person stopped because of peripheral neuropathy. Results suggest only a few people stopped taking cholic acid treatment. The common reason for stopping cholic acid treatment was because of their condition getting worse. Results should be interpreted with caution because studies were small, uncontrolled, unblinded and non-comparative. Some people received additional treatment with ursodeoxycholic acid as well as cholic acid, which may disguise the true treatment effect of cholic acid. The design and conduct of the studies mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions. Cholic acid is licensed for 5 different subtypes of inborn error of bile acid synthesis, but results were not generally reported by subtype, and the subtypes had uneven representation across and within studies.
	Study CAC-002-001	6/10	Indirectly applicable		
Deaths	Heubi et al. 2017	6/10	Directly applicable	B	This outcome considered how many people died during the study. The main study, Heubi et al. 2017, found 7 people with single enzyme deficiency died during cholic acid treatment. Four people had end-stage liver disease at the start of treatment and became worse and 3 people had worsening liver disease. Death was thought not to be related to cholic acid treatment. In study CAC-002-001, 3 people died, 1 because of disease progression and 1 because of thrombosis. No reason was provided in the study for the cause of death for the third person. None of the adverse events leading to death were thought to be related to cholic acid. In the study by Al Hussaini et al. 2017, 4 people died, 2 due to liver failure, 1 person died from severe cardiomyopathy and 1 person died of complications related to
	Study CAC-002-001	6/10	Indirectly applicable		
	Al-Hussaini e al. 2017	5/10	Directly applicable		

					multi-organ primary disease. Results suggest that people commonly died because of their condition and deaths reported in the study were not because of cholic acid treatment. Results should be interpreted with caution because studies were small, uncontrolled, unblinded and non-comparative. Some people received additional treatment with ursodeoxycholic acid as well as cholic acid, which may disguise the true treatment effect of cholic acid. In addition the frequency of death reported in the studies included people with peroxisomal disorders as well as single enzyme deficiency disorders. The design and conduct of the studies mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions. Cholic acid is licensed for 5 different subtypes of inborn error of bile acid synthesis, but results were not generally reported by subtype, and the subtypes had uneven representation across and within studies.

3 Related NICE guidance and NHS England clinical policies

NHS England and NICE have not issued any guidelines or policies on managing inborn errors of primary bile acid synthesis due to 3beta-HSD, 5beta-reductase, sterol 27-hydroxylase (CTX), AMACR and CYP7A1 deficiencies with cholic acid.

4 References

Al-Hussaini A A, Setchell K D. R, Alsaleem B, Heubi J E, Lone K, Davit-Spraul A, and Jacquemin E (2017) Bile Acid Synthesis Disorders in Arabs: A 10-year Screening Study. Journal of Pediatric Gastroenterology and Nutrition 65(6), 613-620

Gonzales Emmanuel, Gerhardt Marie F, Fabre Monique, Setchell Kenneth D. R, Davit-Spraul Anne, Vincent Isabelle, Heubi James E, Bernard Olivier, and Jacquemin Emmanuel (2009) Oral cholic acid for hereditary defects of primary bile acid synthesis: a safe and effective long-term therapy. Gastroenterology 137(4), 1310-3

Heubi J E, Setchell K D. R and Bove K E (2007) Inborn errors of bile acid metabolism. Seminars in Liver Disease 27(3), 282-294

Heubi J E, Bove K E, and Setchell K D. R (2017) Oral Cholic Acid Is Efficacious and Well Tolerated in Patients With Bile Acid Synthesis and Zellweger Spectrum Disorders. Journal of Pediatric Gastroenterology and Nutrition 65(3), 321-326

Subramaniam P, Clayton P, Portmann BC, Mieli-Vergani G, Hadzic N (2010) Variable Clinical Spectrum of the Most Common Inborn Error of Bile Acid Metabolism—3b-hydroxy-D5-C27-steroid Dehydrogenase Deficiency. Journal of Pediatric Gastroenterology and Nutrition 50(1), 61–66

This clinical evidence review has been written by NICE, following the process set out in the standard operating procedure.

Appendix 1 Search strategy

Database: Ovid MEDLINE(R) Epub Ahead of Print; In-Process & Other Non-Indexed Citations; Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)
Platform: Ovid
Version: 1946 - date
Search date: 1st September 2017
Number of results retrieved: 586
Search strategy:

1 exp Cholic Acid/ (1886)
2 cholic acid.tw. (3319)
3 cholan-24-oic acid.tw. (123)
4 chenocholic acid.tw. (0)
5 cholalic acid.tw. (8)
6 cholate.tw. (3277)
7 hydrocholate sodium.tw. (0)
8 "nsc 6135".tw. (0)
9 "nsc6135".tw. (0)
10 trihydroxycholanic acid.tw. (8)
11 trihydroxycholanoic acid.tw. (7)
12 trihydroxycholic acid.tw. (0)
13 tri-saturated bile acid.tw. (0)
14 chobile.tw. (0)
15 chobiol.tw. (0)
16 cholbam.tw. (1)
17 kolbam.tw. (0)
18 orphacol.tw. (0)
19 orphacoldegree.tw. (0)
20 felagol.tw. (0)
21 or/1-20 (6919)
22 exp "Bile Acids and Salts"/ (35226)
23 bile acid.tw. (14556)
24 biliary acid.tw. (60)
25 Cholestanetriol 26-Monooxygenase/ (734)
26 exp "Racemases and Epimerases"/ (5022)
27 Cholesterol 7-alpha-Hydroxylase/ (1360)
28 3-Hydroxysteroid Dehydrogenases/ (3162)
29 exp Oxidoreductases/ (635189)
30 (sterol adj3 hydroxylase).tw. (347)
31 racemase.tw. (1734)
32 epimerase.tw. (2161)
33 AMACR.tw. (499)
34 (cholesterol adj5 monooxygenase).tw. (31)
35 (cholesterol adj5 hydroxylase).tw. (1793)
36 CYP7A1.tw. (968)
37 oxidoreductase.tw. (14387)
38 reductase.tw. (87954)
39 or/22-38 (712481)
40 disorder*.tw. (958777)
41 error*.tw. (255764)
42 deficien*.tw. (452966)
43 defect*.tw. (440853)

44 problem*.tw. (932105)
45 insufficien*.tw. (199418)
46 df.fs. (154320)
47 or/40-46 (2990877)
48 exp Metabolism, Inborn Errors/ (153533)
49 Xanthomatosis, Cerebrotendinous/ (292)
50 cerebrotendinous xanthomatosis.tw. (605)
51 cholestanolosis.tw. (6)
52 ctx.tw. (9622)
53 or/48-52 (163137)
54 21 and 39 and 47 (418)
55 21 and 53 (130)
56 limit 54 to (human and english language) (173)
57 limit 55 to (human and english language) (104)
58 56 or 57 (224)
59 "bile acids and salts"/ or cholic acids/ or cholic acid/ (24108)
60 bile acid*.tw. (21809)
61 cholic acid*.tw. (3408)
62 or/59-61 (34220)
63 df.fs. (154320)
64 cerebrotendinous xanthomatosis.tw. (605)
65 Xanthomatosis, Cerebrotendinous/ (292)
66 or/63-65 (154928)
67 62 and 66 (803)
68 orphacol.tw. (0)
69 kolbam.tw. (0)
70 cholbam.tw. (1)
71 CAC-91-10-10.af. (0)
72 CAC-001-01.af. (0)
73 CAC-002-01.af. (0)
74 or/67-73 (804)
75 74 (804)
76 limit 75 to (english language and humans) (422)
77 58 or 76 (584)
78 dehydrogenase isomerase deficiency in a 23 year old woman.ti. (1)
79 oral cholic acid for hereditary defects of primary bile.ti. (1)
80 familial giant cell hepatitis associated with synthesis.ti. (1)
81 clayton.fa. and "bile acids in liver disease".ti. (1)
82 "cholestatic liver disease in adults may be due to an inherited".ti. (1)
83 potin.fa. and "evaluation du traitement".ti. (0)
84 setchell.fa. and "defects in bile acid synthesis".ti. (0)
85 "variable clinical spectrum of the most common".ti. (1)
86 des acides biliaires primaires.ti. (0)
87 oxidoreductase deficiency in 16 patients with loss.ti. (1)
88 deficiency described in identical twins with neonatal.ti. (1)
89 (bile acid synthetic defects and liver).ti. and "2004".yr. (1)
90 palermo.fa. and "deficiency and steroid metabolism".ti. (1)
91 lemonde.fa. and mutations in srd5b1.ti. (1)
92 ueki.fa. and neonatal cholestatic liver disease in an asian.ti. (1)
93 or/78-92 (12)
94 effects of bile acid therapy in children with defects of primary bile acid.ti. (0)
95 pierre.fa. and "prospective treatment".ti. and "2008".yr. (1)
96 daugherty.fa. and resolution of liver biopsy.ti. (1)
97 vanderpas.fa. and malabsorption of liposoluble.ti. (1)

98 "Determination of cholic acid and chenodeoxycholic acid pool sizes and fractional turnover rates by means".ti. (1)
99 78 or 79 or 83 or 94 or 95 or 96 or 97 or 98 (6)
100 93 or 99 (16)
101 77 or 100 (586)

Database: Embase
Platform: Ovid
Version: 1974 to 31st August 2017
Search date: 1st September 2017
Number of results retrieved: 204
Search strategy:

1 cholic acid/ (5524)
2 cholic acid.tw. (3875)
3 cholan-24-oic acid.tw. (120)
4 chenocholic acid.tw. (0)
5 cholalic acid.tw. (8)
6 cholate.tw. (3457)
7 hydrocholate sodium.tw. (0)
8 "nsc 6135".tw. (0)
9 "nsc6135".tw. (0)
10 trihydroxycholanic acid.tw. (8)
11 trihydroxycholanoic acid.tw. (9)
12 trihydroxycholic acid.tw. (0)
13 tri-saturated bile acid.tw. (0)
14 chobile.tw. (0)
15 chobiol.tw. (0)
16 cholbam.tw. (6)
17 kolbam.tw. (0)
18 orphacol.tw. (3)
19 orphacoldegree.tw. (1)
20 felagol.tw. (0)
21 or/1-20 (9064)
22 bile acid synthesis/ (2352)
23 bile acid.tw. (17869)
24 biliary acid.tw. (72)
25 (sterol adj3 hydroxylase).tw. (409)
26 exp 2 methylacyl coenzyme A racemase/ (755)
27 racemase.tw. (2061)
28 epimerase.tw. (2295)
29 AMACR.tw. (819)
30 cholesterol 7alpha monooxygenase/ (2344)
31 (cholesterol adj5 monooxygenase).tw. (34)
32 (cholesterol adj5 hydroxylase).tw. (2031)
33 CYP7A1.tw. (1379)
34 exp oxidoreductase/ (918253)
35 oxidoreductase.tw. (15376)
36 reductase.tw. (98304)
37 or/22-36 (966965)
38 disorder*.tw. (1239456)
39 error*.tw. (295915)
40 deficien*.tw. (561356)
41 defect*.tw. (514387)

42 problem*.tw. (1114803)
43 insufficien*.tw. (255306)
44 or/38-43 (3569232)
45 *"hereditary bile acid deficiency"/ (1)
46 cerebrotendinous xanthomatosis/ (797)
47 cerebrotendinous xanthomatosis.tw. (722)
48 cholestanolosis.tw. (7)
49 ctx.tw. (14300)
50 or/45-48 (897)
51 21 and 37 and 44 (384)
52 21 and 50 (60)
53 limit 51 to (human and english language) (186)
54 limit 52 to (human and english language) (37)
55 53 or 54 (198)
56 orphacol.tw. (3)
57 kolbam.tw. (0)
58 cholbam.tw. (6)
59 CAC-91-10-10.af. (0)
60 CAC-001-01.af. (0)
61 CAC-002-01.af. (0)
62 or/55-61 (204)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR – 8 of 12, 2017
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – 7 of 12, July 2017
HTA – 4 of 4, October 2016
NHS EED – 2 of 4, April 2015 (legacy database)
Search date: 31st September 2017
Number of results retrieved: CDSR – 4; DARE – 0; CENTRAL – 7; HTA – 2; NHS EED – 0.
Search strategy:

ID Search
#1 [mh "Cholic Acid"]
#2 cholic acid:ti,ab
#3 cholan-24-oic acid:ti,ab
#4 chenocholic acid:ti,ab
#5 cholalic acid:ti,ab
#6 cholate:ti,ab
#7 hydrocholate sodium:ti,ab
#8 "nsc 6135":ti,ab
#9 nsc6135:ti,ab
#10 trihydroxycholanic acid:ti,ab
#11 trihydroxycholanoic acid:ti,ab
#12 trihydroxycholic acid:ti,ab
#13 tri-saturated bile acid:ti,ab
#14 chobile:ti,ab
#15 chobiol:ti,ab
#16 cholbam:ti,ab
#17 kolbam:ti,ab
#18 orphacol:ti,ab

#19 orphacoldegree:ti,ab
#20 felagol:ti,ab
#21 {or #1-#20}
#22 [mh "Bile Acids and Salts"]
#23 bile acid:ti,ab
#24 biliary acid:ti,ab
#25 [mh ^"Cholestanetriol 26-Monooxygenase"]
#26 [mh "Racemases and Epimerases"]
#27 [mh ^"Cholesterol 7-alpha-Hydroxylase"]
#28 [mh ^"3-Hydroxysteroid Dehydrogenases"]
#29 [mh Oxidoreductases]
#30 (sterol near/3 hydroxylase):ti,ab
#31 racemase:ti,ab
#32 epimerase:ti,ab
#33 AMACR:ti,ab
#34 (cholesterol near/5 monooxygenase):ti,ab
#35 (cholesterol near/5 hydroxylase):ti,ab
#36 CYP7A1:ti,ab
#37 oxidoreductase:ti,ab
#38 reductase:ti,ab
#39 {or #22-#38}
#40 disorder*:ti,ab
#41 error*:ti,ab
#42 deficien*:ti,ab
#43 defect*:ti,ab
#44 problem*:ti,ab
#45 insufficien*:ti,ab
#46 Any MeSH descriptor with qualifier(s): [Deficiency - DF]
#47 {or #40-#46}
#48 [mh "Metabolism, Inborn Errors"]
#49 [mh ^"Xanthomatosis, Cerebrotendinous"]
#50 cerebrotendinous xanthomatosis:ti,ab
#51 cholestanolosis:ti,ab
#52 ctx:ti,ab
#53 {or #48-#52}
#54 #21 and #39 and #47
#55 #21 and #53
#56 #54 or #55
#57 [mh ^"bile acids and salts"]
#58 [mh ^"cholic acids"]
#59 [mh ^"cholic acid"]
#60 bile acid*:ti,ab
#61 cholic acid*:ti,ab
#62 {or #57-#61}
#63 Any MeSH descriptor with qualifier(s): [Deficiency - DF]
#64 cerebrotendinous xanthomatosis:ti,ab
#65 [mh "Xanthomatosis, Cerebrotendinous"]
#66 {or #63-#65}
#67 #62 and #66
#68 orphacol:ti,ab
#69 kolbam:ti,ab
#70 cholbam:ti,ab
#71 CAC-91-10-10
#72 CAC-001-01

#73 CAC-002-01
#74 {or #67-#73}
#75 #56 or #74
#76 "evaluation du traitement":ti
#77 "defects in bile acid synthesis":ti
#78 "des acides biliaires primaires":ti
#79 "effects of bile acid therapy in children with defects of primary bile acid":ti
#80 {or #75-#79}

Appendix 2 Study selection

The search strategy presented in appendix 1 yielded 710 studies. These were screened on titles and abstracts in EPPI Reviewer according to the following inclusion/exclusion criteria:

Sifting criteria	Inclusion	Exclusion
Population	People aged 1 month or older with inborn errors in primary bile acid synthesis due to • 3-beta-hydroxy-delta5-C27-steroid oxidoreductase deficiency; or • delta4-3-oxosteroid 5-beta-reductase deficiency; or • sterol 27-hydroxylase (presenting as CTX) deficiency; or • 2- (or alpha-) methylacyl-CoA racemase deficiency (AMACR); or • cholesterol 7alpha-hydroxylase (CYP7A1) deficiency.	Non-humans People with other bile acid synthesis disorders other than single enzyme defects
Intervention	Cholic acid with or without other treatments	Chenodeoxycholic acid Ursodeoxycholic acid
Comparator	Standard care without cholic acid Other bile acids either as monotherapy or combination therapy Neutraceuticals	None
Outcomes	• Mortality • Liver disease (including need for liver transplantation and change in liver histology) • Neurological disease including cognitive dysfunction • Height and weight change • Complications such as rickets, bleeding diathesis, night blindness, and neuroaxonal dystrophy • Cataract, diarrhea, ataxia with xanthoma for CTX • Laboratory test results (for example, bile acids, liver transaminases and bilirubin)	

	• Need for vitamin supplementation • Avoidance of atherosclerosis • For CTX, regression of xanthomata in CTX • Disability measures.	
Other		Non-English language papers Conference abstracts and posters Duplicate papers Review articles, opinion pieces, commentaries, epidemiological studies and burden of disease studies Case reports and case series with less than 14 people with BASDs Studies looking at diagnosis, complications, presentations and genetic mutations, rather than treatment outcomes

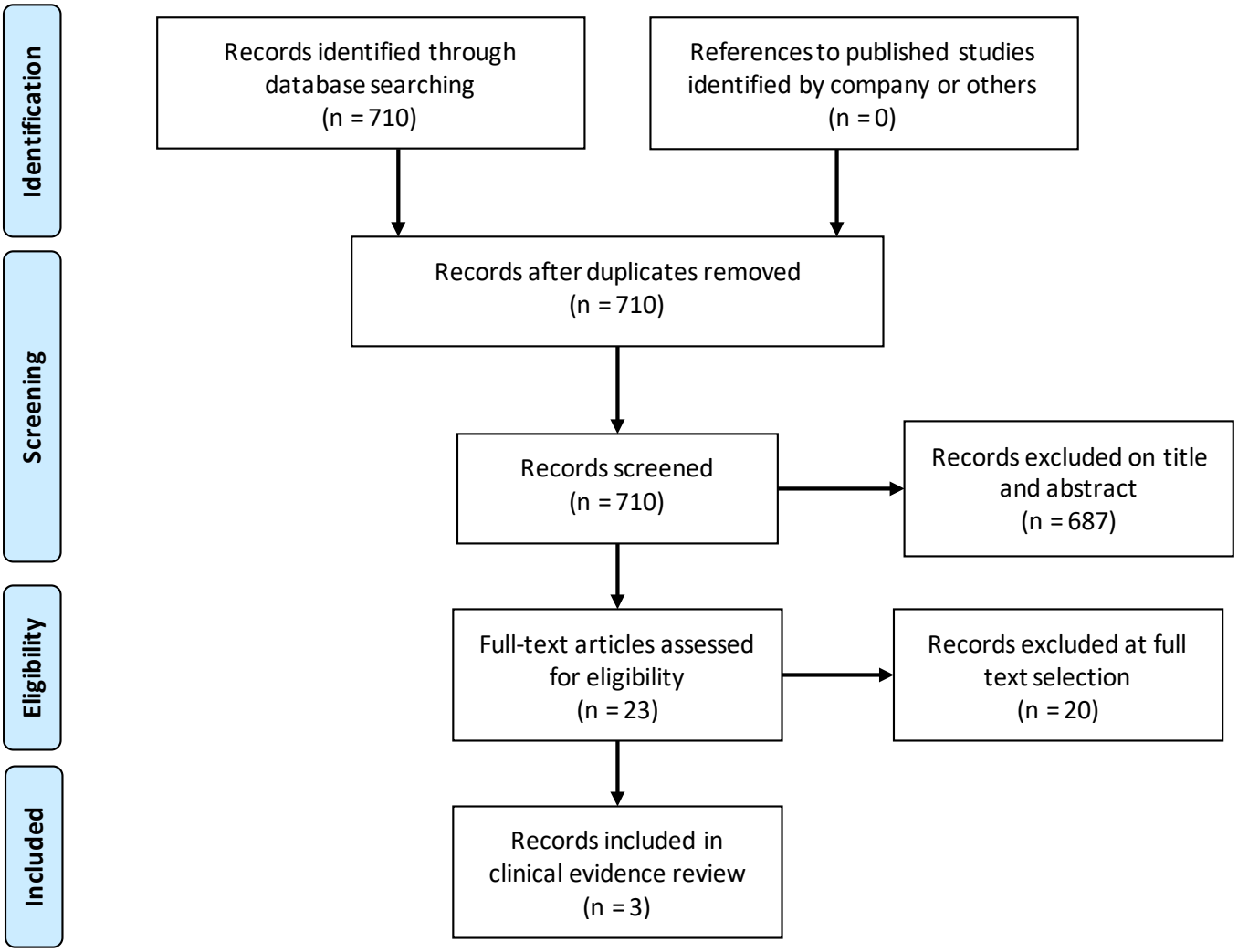
Twenty-three full text references were obtained and assessed for relevance. Of these, 3 are included in the evidence summary. The remaining 20 references were excluded and are listed in table 3.

Table 3 Studies excluded at full text

Study reference	Reason for exclusion
Al-Hussaini A, Alsaleem B, and Lone K (2016) Clinical, histopathological and molecular genetics of children with inborn errors of bile acid synthesis and liver disease: Results from an eight years prospective study. Journal of Pediatric Gastroenterology and Nutrition 62, 498	Abstract
Al-Hussaini A, Setchell K, AlSaleem B, Heubi J, Lone K, Davit-Spraul A, and Jacquemin E (2017) Bile acid synthesis disorders in arabs: A 10-year prospective screening study using serum total bile acids with confirmatory mass spectrometry and genetic analyses for diagnosis and follow-up to cholic acid therapy. Journal of Pediatric Gastroenterology and Nutrition 65(Supplement 2), S170	Abstract
Anonymous (2015) Cholic acid (ORPHACOLdegree): Decisive in some hereditary bile acid deficiencies. Prescrire International 24(157), 36-37	Review article
Anonymous (2016) In brief: Cholic acid (Cholbam) for bile acid synthesis disorders. The Medical letter on drugs and therapeutics 58(1493), 56	Medical letter
Bove Kevin E, Heubi James E, Balistreri William F, and Setchell Kenneth D. R (2004) Bile acid synthetic defects and liver disease: a comprehensive review. Pediatric and developmental pathology : the official journal of the Society for Pediatric Pathology and the Paediatric Pathology Society 7(4), 315-34	Review paper
Bjorkhem I (1994) Inborn errors of metabolism with consequences for bile acid biosynthesis. A minireview. Scandinavian journal of gastroenterology. Supplement 204, 68-72	Review paper
Cheng Jeffrey B, Jacquemin Emmanuel, Gerhardt Marie, Nazer Hisham, Cresteil Daniele, Heubi James E, Setchell Kenneth D. R, and Russell David W (2003) Molecular genetics of 3beta-hydroxy-Delta5-C27-steroid oxidoreductase deficiency in 16 patients with loss of bile acid synthesis and liver disease. The Journal of clinical endocrinology and metabolism 88(4), 1833-41	No relevant outcomes reported
Cerqueira Ana Claudia Rodrigues de, Nardi Antonio Egidio, and Bezerra Jose Marcelo Ferreira (2010) Cerebrotendinous xanthomatosis: a treatable hereditary neuro-metabolic disease. Clinics (Sao Paulo, and Brazil) 65(11), 1217-8	Letter describing 1 case report
Clayton P T (1991) Inborn errors of bile acid metabolism. Journal of inherited metabolic disease 14(4), 478-96	Review article reporting less than 15 cases of BASDs
Gonzales Emmanuel, and Jacquemin Emmanuel (2011) Primary bile acid therapy during pregnancy in patients with 3beta-hydroxy-DELTA5 -C27 -steroid	Letter to the editor

oxidoreductase deficiency. Pediatrics international : official journal of the Japan Pediatric Society 53(5), 792	
Gonzales Emmanuel, Cresteil Daniele, Baussan Christiane, Dabadie Alain, Gerhardt Marie-Francoise, and Jacquemin Emmanuel (2004) SRD5B1 (AKR1D1) gene analysis in delta(4)-3-oxosteroid 5beta-reductase deficiency: evidence for primary genetic defect. Journal of hepatology 40(4), 716-8	Case report of 2 people with BASDs
Hofmann A F (2017) Bile Acid Replacement in Bile Acid Synthesis Defects. Journal of Pediatric Gastroenterology and Nutrition 65(6), e134-e135	Letter to the editors
Jacquemin E, and Gonzales E (2017) Cholic Acid to Treat HSD3B7 and AKR1D1 Deficiencies. Journal of Pediatric Gastroenterology Nutrition 65(6), e134-e135	Letter to the editors
Jacquemin E, Setchell K D, O'Connell N C, Estrada A, Maggiore G, Schmitz J, Hadchouel M, and Bernard O (1994) A new cause of progressive intrahepatic cholestasis: 3 beta-hydroxy-C27-steroid dehydrogenase/isomerase deficiency. The Journal of pediatrics 125(3), 379-84	Intervention not relevant
Kobayashi M, Koike M, Sakiyama M, Okuda S, Okuda M, Tanaka T, Unno A, Nittono H, Takei H, Murai T, Yoshimura T, and Kurosawa T (2000) 3beta-hydroxy-delta5-C27-steroid dehydrogenase/isomerase deficiency in a 23-year-old woman. Pediatrics international : official journal of the Japan Pediatric Society 42(6), 685-8	Case report of 1 person with BASD
Koopman B J, Wolthers B G, van der Molen , J C, van der Slik , W , Waterreus R J, van Spreeken , and A (1988) Cerebrotendinous xanthomatosis: a review of biochemical findings of the patient population in The Netherlands. Journal of inherited metabolic disease 11(1), 56-75	Review article reporting treatment with cholic acid in less than 14 cases of BASDs
Koopman B J, Wolthers B G, van der Molen , J C, and Waterreus R J (1985) Bile acid therapies applied to patients suffering from cerebrotendinous xanthomatosis. Clinica chimica acta, and international journal of clinical chemistry 152(1-2), 115-22	Review article reporting treatment with cholic acid in less than 14 cases of BASDs
Suchy F J (1993) Bile acids for babies? Diagnosis and treatment of a new category of metabolic liver disease. Hepatology (Baltimore, and Md.) 18(5), 1274-7	Editorial
Waterreus R J, Koopman B J, Wolthers B G, and Oosterhuis H J (1987) Cerebrotendinous xanthomatosis (CTX): a clinical survey of the patient population in The Netherlands. Clinical neurology and neurosurgery 89(3), 169-75	Review article reporting treatment with cholic acid in less than 14 cases of BASDs
Waterreus R J, and Koopman B J (1987) Cerebrotendinous xanthomatosis: more on diagnosis and treatment. Neurology 37(6), 1091-2	Letter to the editor

Figure 1 Flow chart of included studies



Appendix 3 Evidence tables

Table 4 Heubi et al. 2017

Study reference	Heubi JE, Bove KE, and Setchell KDR (2017) Oral cholic acid is efficacious and well tolerated in patients with bile acid synthesis and Zellweger spectrum disorders. Journal of Pediatric Gastroenterology and Nutrition 65(3): 321-326
Unique identifier	NCT00007020, study CAC-91-10-10
Study type (and NSF-LTC study code)	Phase 3, open-label, single-arm, non-randomized, non-comparative, compassionate treatment study[a] P1 Primary research using quantitative approaches
Aim of the study	To evaluate the efficacy and safety of oral cholic acid in people with bile acid synthesis disorders due to single enzyme deficiencies[b] and Zellwegers spectrum disorders .
Study dates	January 1992 to December 2009
Setting	The study started at the Cincinnati Children's Hospital Medical Centre, USA but was later expanded to enrol people from other sites[c]
Number of participants	85 patients (n=54 with single enzyme deficiencies, n=31 with Zellwegers spectrum disorders – intention to treat population)[d]
Population	The mean age was 2 years at diagnosis and 3 years at the start of treatment[e]. 59% were male and 36% were female. The mean weight and height percentiles were 39% and 33% respectively. The majority of children with single enzyme deficiency presented with 3beta-HSD deficiency (n=35 (median age 37 months) or 5beta-reductase deficiency (n=10) (median age 3 months). Five had sterol 27-hydroxylase deficiency (presenting as CTX) and 1had AMACR deficiency. Two children with single enzyme deficiency were classed as 'others' and 1 was classed as 'unknown'.
Inclusion criteria	People with a diagnosis of an inborn error of bile acid synthesis confirmed by urine FAB-MS analysis and the presence of atypical bile acids characteristic of the specific defect in bile acid synthesis.
Exclusion criteria	No specific exclusion criteria were defined for the study
Intervention(s)	Cholic acid 10 to 15 mg/kg daily was given either as 1 dose or in divided doses twice daily as capsules emptied into food, or as a liquid formulation (15 mg/mL) for those who could not swallow capsules. In the original study protocol, a combination of ursodeoxycholic acid and cholic acid were included as the intervention. However, at some point during the study, ursodeoxycholic acid was stopped because analysis of urinary bile acids suggested that ursodeoxycholic acid could interfere with the intestinal absorption of cholic acid. Cholic acid was given as monotherapy thereafter.
Comparator(s)	None
Length of follow-up	The study was conducted over 18 years. The authors state that there was a variable distribution of pre- and post-treatment visits. One pre- and

	1 post-treatment visit were selected and used to assess the impact of cholic acid on the main outcomes. Mean duration of treatment in the safety set[f] was 145 weeks (range 0 to 545 weeks).
Outcomes	Primary outcomes: • Changes in the worst pre- to best post-treatment in: – urinary bile acid metabolites – liver chemistries (ALT and AST) – growth measurements (height and weight)
	Secondary outcomes: • Changes in the worst pre- to best post-treatment in: – serum bilirubin (total and direct) – liver histology (for participants with liver biopsies)
	Safety outcomes: • Deaths • Adverse events (included serious) • Treatment-related adverse events (included serious) • Adverse events leading to discontinuation of study drug
Source of funding	The study was supported by Cincinnati Children's Research Foundation and the National Centre for Advancing Translational Sciences of the National Institutes of Health. Funding for writing and editorial support was provided by Retrophin Inc. to Scientific Communications Group.
Abbreviations	3beta-HSD, 3-beta-hydroxy-delta5-C27-steroid oxidoreductase; 5beta-reductase, delta4-3-oxosteroid-5-beta reductase; ALT, alanine aminotransferase; AMACR, 2-methylacyl-CoA racemase; AST, aspartate aminotransferase; CYP7A1, cholesterol 7alpha-hydroxylase.
Comments	[a] This was initially an investigator-initiated, compassionate use program and then transitioned into a formal clinical trial program [b] The study also included people with Zellweger spectrum disorders (a type of peroxisomal disorder). The focus of this evidence review is only in people with single enzyme deficiencies [c] The paper does not specify the location of the other sites used in the study. Population seems mainly representative of a single centre in the US. [d] The number of people with single enzyme deficiency was different in the total enrolled (n=63) compared with the intention to treat population (n=54). It was not clear in the paper the reason for this difference. For the purpose of this evidence review, the intention to treat population number has been used, as the total of each single enzyme deficiency was the same as the total for the intention to treat population. [e] The mean age includes people with single enzyme deficiencies and Zellweger spectrum disorders [f] The safety set consisted of children with available treatment start and

	stop dates

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	The research questions are stated and the design is clearly stated.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	Given the nature of these diseases and understanding of their natural histories there was never any consideration for performing a placebo-controlled trial because it was considered unethical. The study was open-label and uncontrolled, and subject to bias and confounding. Therefore, it is insufficient to reliably answer the research questions, and the results should be interpreted with caution.
3. Are the methods clearly described?	1/2	The methods are mostly described, however follow-up of patients at particular time points is not very clear. The authors state that the study design was not structured with the rigor now required in contemporary studies. Therefore the weaknesses in the design and conduct of the study are acknowledged.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	The data are adequate to support limited conclusions, based on the uncontrolled nature of the study. There were few numbers of participants included to draw firm conclusions on. The marketing authorisation was granted under exceptional circumstances based partly on this study, subject to collection of long-term efficacy and safety data.
5. Are the results generalisable?	1/2	The results are partly generalisable to the UK as the study was carried out in a

		single centre in the US.
Total	6/10	
Applicability*	Directly / indirectly applicable	Directly applicable: Although the study included people with single enzyme defect disorders and Zellwegers spectrum disorders, the results for each class were reported separately. This allowed focussing on people with the indication and characteristics of interest.

Table 5 Study CAC-002-001

Study reference	An open-label, single-centre, nonrandomized continuation study of cholic acid capsules in subjects with inborn errors of bile acid synthesis.
Unique identifier	CAC-002-001, also CAC-002-01
Study type (and NSF-LTC study code)	Phase 3, open-label, single-arm, non-randomised, non-comparative study. The study was a continuation study that included eligible patients who had previously received cholic acid in studies CAC-91-10-10 (see evidence table 4) or CAC-001-01 (NCT01115582)[a] and newly diagnosed patients P1 Primary research using quantitative approaches
Aim of the study	To evaluate the therapeutic efficacy and safety of cholic acid in people with identified inborn errors of bile acid metabolism
Study dates	January 2010 to September 2012
Setting	Cincinnati Children's Hospital Medical Centre (CCHMC), USA
Number of participants	41 patients, of which 31 came from study CAC-91-10-10 and were already taking cholic acid and 10 patients were treatment naïve
Population	Patients with single enzyme defects presented with 3beta-HSD deficiency (n=21), 5beta-reductase deficiency (n=4) and CTX deficiency (n=4). 12 patients had peroxisomal disorders.
Inclusion criteria	Not reported
Exclusion criteria	Not reported.
Intervention(s)	Cholic acid 10 to 15 mg/kg daily (CCHMC formulation and the commercial formulation)
Comparator(s)	None
Length of follow-up	33 months
Outcomes	Primary outcome:

	Changes in baseline to the worst post-baseline response in: • Urine bile acids • Transaminases • Bilirubin • Height and weight percentiles
	Safety outcomes: • Treatment-emergent adverse events • Study drug discontinuation • Treatment-emergent serious adverse events • Serious adverse events • Deaths
Source of funding	Not known
Abbreviations	3beta-HSD, 3-beta-hydroxy-delta5-C27-steroid oxidoreductase; 5beta-reductase, delta4-3-oxosteroid-5-beta reductase; CTX, cerebrotendinous xanthomatosis
Comments	[a] Study CAC-001-10 is an unpublished study that compared the efficacy of different cholic acid preparations (to be marketed preparation versus currently used preparation from the medical centre). The EPAR includes this study as part of the clinical efficacy review.

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	Note that this study has not yet been published in a peer reviewed journal. Information was obtained from the EPAR, which reports data that was assessed when the medicine was assessed for a marketing authorisation In the EPAR, the research question and design are described.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	The study was a non-randomised, non-comparative continuation study, which is subject to bias and confounding. Therefore, it is insufficient to reliably answer the research questions, and the results should be interpreted with caution. The EPAR states that a controlled clinical study would not be feasible given the rare condition with limited treatment options.
3. Are the methods clearly described?	1/2	The methods are only partially described.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	The data are adequate to support limited conclusions, based on the uncontrolled nature of the study. A marketing authorisation was granted under exceptional circumstances based partly on this study, subject to collection of long-term efficacy and safety data.
5. Are the results generalisable?	1/2	The results are partly generalisable to the UK as the study was carried out in a single centre in the US.

Total	6/10	
Applicability	Directly / indirectly applicable	Indirectly applicable: an indirect study that focusses on people with the single enzyme defect disorders and peroxisomal disorders and reported combined results.

Table 6 Al-Hussaini et al. 2017

Study reference	Al-Hussaini AA, Setchell K D. R, Alsaleem B et al.(2017) Bile acid synthesis disorders in Arabs: a 10-year screening study. Journal of Pediatric Gastroenterology and Nutrition 65(6); 613-620
Unique identifier	None
Study type (and NSF-LTC study code)	Prospective observational study P1 Primary research using quantitative approaches
Aim of the study	To screen children with cholestasis or unexplained liver disease for BASD and, in children with confirmed BASD, to evaluate the effectiveness of cholic acid therapy
Study dates	2007 to 2016
Setting	Tertiary referral centre in Saudi Arabia
Number of participants	A total of 626 children were screened (450 with infantile cholestasis). 15 children were diagnosed with BASD and treated. Out of the 15 children (from 9 families) with BASD, 11 had 3beta-HSD deficiency, 3 had 5beta-reductase deficiency and 1 had Zellweger spectrum disorder.
Population	Children with age range of 1 month to 8 years. There were 10 boys and 5 girls with BASD.
Inclusion criteria	Infants and children (birth to 14 years) presenting with cholestasis[a], chronic hepatitis, cirrhosis, liver failure[b], or vitamin D –resistant rickets and children identified with potential BASD
Exclusion criteria	Children not having BASD
Intervention(s)	Oral cholic acid 15 mg/kg in 2 divided doses[c,d]
Comparator(s)	None
Length of follow-up	10 years
Outcomes	Primary outcome: • Response to cholic acid therapy, defined as complete resolution of cholestasis and/or liver dysfunction and survival with native liver
	Secondary outcomes: • Improvement to liver chemistry tests

	• Improvement in liver histopathology
	Safety outcomes: Not listed
Source of funding	Unknown
Abbreviations	3beta-HSD, 3-beta-hydroxy-delta5-C27-steroid oxidoreductase; 5beta-reductase, delta4-3-oxosteroid-5-beta reductase; BASD, bile acid synthesis disorders; INR, international normalised ratio;
Comments	[a] Clinically defined as the presence of jaundice and/or acholic stools with a conjugated bilirubin of more than 20 micromoles/L, or more than 15% of the total bilirubin concentration [b] An INR of greater than or equal to 2 and unresponsive to vitamin K injection [c] Cholic acid was first supplied from Cincinnati Children's Hospital Medical Centre and then by Special Laboratories for special products company Ltd UK [d] All children were receiving treatment with ursodeoxycholic acid before BASD was diagnosed. All children switched over to cholic acid monotherapy except for 2 who continued with ursodeoxycholic acid for 20 and 30 months. It was not clear in the study if the 2 children were taking ursodeoxycholic acid alongside cholic acid.

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	The research question and design are described in the study.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	The study was an observational study, which is subject to bias and confounding. Therefore, it is insufficient to reliably answer the research questions, and the results should be interpreted with caution. A controlled clinical study would not be feasible given the rare condition with limited treatment options.
3. Are the methods clearly described?	1/2	The methods are only partially described. There is no acknowledgement of bias and confounding and no mention of statistical analyses of results.
4. Are the data adequate to support the authors' interpretations / conclusions?	0/2	The data are not adequate to support the conclusions, based on the uncontrolled nature of the study and broad outcomes. The main outcome measured response to cholic acid treatment by looking at cholestasis, liver dysfunction and survival with native liver. The conclusion with regard to the effect of treatment using the results of the outcome measure relating to cholestasis and liver dysfunction is unclear in the authors' discussion.
5. Are the results generalisable?	1/2	The results are only partly generalisable to the UK as the study was carried out in a single centre in Saudi Arabia.
Total	5/10	

Applicability*	Directly / indirectly applicable	Directly applicable

Table 7 Gonzales et al. 2009

Study reference	Gonzales E , Gerhardt MF, Fabre M et al. , (2009) Oral cholic acid for hereditary defects of primary bile acid synthesis: a safe and effective long-term therapy. Gastroenterology 137(4); 1310-3
Unique identifier	Clinical trial registration number CRC920608, PHRC P930304 and AOB94024
Study type (and NSF-LTC study code)	Prospective observational study P1 Primary research using quantitative approaches
Aim of the study	To evaluate the long-term effectiveness and safety of cholic acid treatment in people with 3beta-HSD and 5beta-reductase deficiencies
Study dates	1993 to 2007
Setting	Pediatric Hepatology Unit of Bicêtre Hospital, France
Number of participants	15 children form 10 families
Population	Children were at a median age of 3.9 years (range 0.3 to 13.1 years) when cholic acid treatment was started. 13 children had 3beta-HSD deficiency and 2 children (twins) had 5beta-reducatse deficiency. 4 were male and 11 were female. Children were from Portugal (n=2), Chile (n=1) Italy (n=2), France (n=8) and France-Senegal (n=2).
Inclusion criteria	Children with confirmed BASDs
Exclusion criteria	Unknown
Intervention	Oral cholic acid in 2 divided doses, initial mean daily dose was 13 mg/kg and at last evaluation was 6 mg/kg[a,b]
Comparator(s)	None
Length of follow-up	Median follow-up with treatment was 12.4 years (range 5.6 to 15 years)[c]
Outcomes	Outcomes[d]: The study reports the following initial and follow-up evaluations during treatment: • physical examination • blood liver biochemistry tests • abdominal ultrasonography • urine and serum bile acid analyses[e] • liver histology[f]
Source of	Supported by the Assistance Publique - Hôpitaux de Paris in Paris,

funding	France
Abbreviations	3beta-HSD, 3-beta-hydroxy-delta5-C27-steroid oxidoreductase; 5beta-reductase, delta4-3-oxosteroid-5-beta reductase; BASD, bile acid synthesis disorders; FAB-MS, fast atom bombardment mass spectrometry; GC-MS, gas chromatography mass spectrometry;
Comments	[a] After initial treatment, the doses of cholic acid were adjusted individually based on the results of the follow-up urinary bile acid analyses by mass spectrometry and serum liver biochemistries. Doses for the different deficiencies were reported to be 14.2 mg/kg and 10 mg/kg in 3beta-HSD and 5beta-reductase deficiencies, respectively [b] 8 children initially received oral ursodeoxycholic acid as monotherapy before diagnosis of a BASD was established. These children received treatment with ursodeoxycholic acid for the first 6 to 14 months of treatment with cholic acid to allow tapering of ursodeoxycholic acid [c] After starting cholic acid treatment, the children were seen at least every 3 months during the first year, every 6 months during the next 4 years, and every year thereafter [d] Primary, secondary and safety outcomes were not clearly defined in the study [e] Using FAB-MS and/or GC-MS [f] Liver biopsies were analysed by the same pathologist. See the paper for tests used

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**
1. Are the research questions/aims and design clearly stated?	2/2	The research questions are stated and the design is clearly stated.
2. Is the research design appropriate for the aims and objectives of the research?	1/2	The study was an observational study, which is subject to bias and confounding. Therefore, it is insufficient to reliably answer the research questions, and the results should be interpreted with caution. A controlled clinical study would not be feasible given the rare condition with limited treatment options.
3. Are the methods clearly described?	1/2	The methods are mostly described, however the main outcomes of interest were unclear in the study. In addition, there is no acknowledgement of bias and confounding in the methods or discussion.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	The data are adequate to support limited conclusions based on the uncontrolled nature of the study. There were few numbers of participants included to draw firm conclusions from.
5. Are the results generalisable?	1/2	The results are partly generalisable to the UK as the study was carried out in a single centre in France.
Total	6/10	
Applicability	Directly / indirectly applicable	Directly applicable

Appendix 4 Results tables

Table 8 Heubi et al. 2017

	Cholic acid[a]	
Primary outcomes		
N	**43[b]**	**Analysis**
Urinary bile acid metabolites[c,d]		
Percentage of patients with normal atypical bile acid excretion	Pre-treatment: 2.3%	p<0.0001[e]
	Post-treatment: 65.1%	
Percentage of patients with a slight abnormality in atypical bile acid excretion	Pre-treatment: 7%	
	Post-treatment: 14%	
Percentage of patients with a significant abnormality in atypical bile acid excretion	Pre-treatment: 18.8%	
	Post-treatment: 7%	
Percentage of patients with a marked abnormality in atypical bile acid excretion	Pre-treatment: 72.1%	
	Post-treatment: 14%	
Liver chemistries[f]		
Percentage of patients with AST at normal level	Pre-treatment: 18.4%	p<0.0001[e]
	Post-treatment: 85%	
Percentage of patients with AST at ≥2 times the ULN	Pre-treatment: 55.3%	
	Post-treatment: 5%	
Percentage of patients with ALT at normal level	Pre-treatment: 22.5%	p<0.0001[e]
	Post-treatment: 87.5%	
Percentage of patients with ALT at ≥2 times the ULN	Pre-treatment: 52.5%	
	Post-treatment: 5%	
Growth measurements[g]		
Mean height percentile	Pre-treatment: 37.2	p=not significant
	Post-treatment: 49.5	
Mean weight percentile	Pre-treatment: 31.1	p=0.006[h]
	Post-treatment: 54.9	
Safety and tolerability outcomes		

N	50[i]
Number of adverse events	44 (n=21)
Number of serious adverse events	6 (n=5)
Number of treatment-related adverse events	3 (n=2)[j]
Number of serious treatment-related adverse events	0
Number of adverse events leading to drug discontinuation	3 (n=3)
Number of deaths	7[k]

[a] Administered orally 10 to 15 mg/kg daily

[b] Primary analysis was based on the modified intention to treat population that included all patients who received cholic acid and had at least 1 pre- and post-treatment outcome assessment for urine bile acid analysis. Results shown are for worst pre- to best post-treatment. The time of pre- and post-treatment is unclear in the study

[c] Scoring system based on a signal/noise ratio identified by the FAB-MS at baseline and post-treatment. These were assessed as normal (score 0) or as showing slight (score 1), significant (score 2), or marked (score 3) increases in the levels of atypical bile acids

[d] Sensitivity analysis of the worst pre-treatment to the worst post-treatment results and the best pre-treatment to the best post-treatment results showed statistically significant improvements in urine bile acid scores

[e] P-value is from a Cochran-Mantel-Haenszel chi-square test with modified ridit scoring

[f] Serum levels taken were at baseline and at regular intervals during treatment. A value of 50 IU/L was selected as the ULN for AST and ALT

[g] Taken at baseline and at intervals determined by the attending physician using 'standard clinical methods' during treatment.

[h] The p values are from t-tests.

[i] Safety population included all patients who received at least 1 dose of cholic acid. Number of patients with single enzyme deficiency in the safety population is taken from the EPAR:Kolbam as not reported by Heubi et al. 2017

[j] Malaise and jaundice reported in 1 patient and skin lesion in 1 patient

[k] Four patients with 5beta-reductase deficiency had end-stage liver disease at the time of diagnosis and start of treatment, with deterioration despite therapy. Three patients had worsening liver disease (1 with Smith-Lemli-Opitz syndrome, 1 with 3beta-HSD deficiency; 1 with CYP7B1 deficiency). The patient with CYP7B1 deficiency was unresponsive to cholic acid and died of post-liver transplant complications.

Abbreviations

3beta-HSD, 3-beta-hydroxy-delta5-C27-steroid oxidoreductase; 5beta-reductase, delta4-3--oxosteroid-5-beta reductase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FAB-MS. fast atom bombardment ionisation mass spectrometry; ULN,

upper limit of normal;

Table 9 Study CAC-002-001

	Cholic acid[a]	
Primary outcomes		
N	**41[b,c]**	**Analysis**
Urinary bile acid scores[d]		
Percentage of patients with a normal, slight, significantly or marked abnormal atypical bile acid score	Baseline: not reported for each category Best or worst post-baseline response: not reported for each category	No statistically significant changes in urine bile acid scores reported were between baseline and worst post-baseline response for the overall population. In the baseline to best post-treatment analysis, a non-statistically significant increase in the percentage of participants with a normal bile acid score and a non-statistically significant decrease in the percentages of patients with marked or significant elevation in atypical bile acids were reported in the EPAR. These results reached statistical significance in the EE[e] population (p-value not reported).
Transaminases[f]		
Percentage of patients with AST at normal level or with AST at ≥2 times the ULN	Baseline: not reported for each category Best or worst post-baseline response: not reported for each category	No statistically significant changes were seen in the baseline to worst post-baseline analysis. AST values improved with statistical significance from baseline to the best post-baseline assessment ($p < 0.05$).
.	Baseline: not reported for each category Best or worst post-baseline response: not reported for each category	No statistically significant changes were seen in the baseline to worst post-baseline analysis. In the baseline to best post-baseline value analysis, there was a non-statistically significant increase in the number of patients with ALT values less than ULN and a non-statistically significant decrease in the number of patients with values more than or equal to 2 times the ULN reported in the EPAR.
Bilirubin		

Mean change in total bilirubin	Baseline: not reported for each category Best or worst post-baseline response: not reported for each category	Mean change was reported to be stable in the baseline to worst post-baseline value analysis (0.1 mg/dL; range of changes −1.9 to 1.6 mg/dL). Mean change was reported to decrease in the baseline to best post-baseline value analysis (−0.8 mg/dL; range −12.0 to 1.6 mg/dL) Significance was not reported in the EPAR.
Height and weight percentiles		
Mean height percentile	Baseline: not reported Post-baseline: not reported	Both height and weight percentiles decreased slightly in the baseline to worst post-baseline value analysis and increased slightly in the baseline to best post-baseline value analysis. None of the changes were statistically significant.
Mean weight percentile	Baseline: not reported Post-baseline: not reported	
Safety and tolerability outcomes		
N	**Not reported[c,g]**	
Number of treatment-related adverse events	2[h]	
Number of serious adverse events	7[i]	
Number of adverse events leading to drug discontinuation	4[j]	
Number of deaths	3[k]	

[a] Administered orally 10 to 15 mg/kg daily

[b] The intent-to-treat (ITT) population was the main analysis set for efficacy analyses. The ITT population included patients who provided consent and had at least 1 round of study evaluations. The patients included did not follow a fixed visit schedule and so analyses of changes from baseline to a given time point were not feasible

[c] Included patients with single enzyme defects disorders and peroxisomal disorders who were on cholic acid before the study and also treatment naïve patients. Results were not reported separately for each disorder.

[d] Method of analysis was not reported in the EPAR

[e] Efficacy evaluable (EE) population included all participants who for any efficacy end-point had both a baseline and at least 1 post-baseline assessment

[f] The ULN for AST and ALT was not reported in the EPAR

[g] The number of patients in the safety population was not clearly reported. The safety population included patients who received at least 1 dose of cholic acid

[h] Reported to be mild peripheral neuropathy and mild nausea

[i] Disease progression frequently reported (2 with single enzyme deficiency and 2 with

peroxisomal disorder), others reported to only occur once. [j] Disease progression in 3 patients and peripheral neuropathy in 1 patient [k] Disease progression in 2 patients (1 patient had multisystem failure and 1 patient had thrombosis post-liver transplant). No reason was documented for the other patient. Out of the 3 patients who died, 1 had single enzyme deficiency.
Abbreviations ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Table 10 Al-Hussaini et al. 2017

	Cholic acid
Primary outcome	
N	**15[a]**
Response to treatment[b]	• The clinical condition of 12 children was reported to be improved during treatment with cholic acid. • 11 children survived and were reported to have normal liver chemistries after a median follow-up period of 4.5 years (range 1 to 11.5 years). • Out of the 11 that survived, 10 had their native liver and 1 had a liver transplant 2 months after starting treatment with cholic acid. • Fat-soluble vitamins, with supplementation, were reported to be normal in the 11 children who survived. • Jaundice was reported to disappear within a few weeks and the median time interval to normalise liver enzymes was reported to be 3 months (range 1 to 18 months) • Splenomegaly and hepatomegaly were reported to resolve slowly after starting treatment with cholic acid, taking several months or years to improve.
Secondary outcomes	
N	**15[a]**
Liver chemistries	• The authors report a marked reduction in atypical urinary bile acid metabolites after starting cholic acid, which was concomitant with improvement of cholestasis. • LFTs for 2 children were reported. It took 18 months for LFTs to normalise in 1 child because of poor compliance. Another child discontinued treatment and after 2 years his serum liver chemistries and fat-soluble vitamin levels were reported to be normal alongside his urine analysis with low levels of 3-oxo-delta4-cholenoic acids.

Liver biopsies	• The authors reported that 5 follow-up liver biopsies were performed at a median time of 2 years (range 0.5 to 5 years) after starting cholic acid treatment. The biopsies were reported to show significant histological improvement with reduced parenchymal inflammation, loss of giant-cells and regression of portal fibrosis.
Safety outcome	
N	**15[a]**
Death	• 4 were reported, 2 due to liver failure[c], 1 due to severe cardiomyopathy[d] and 1 due to complication related to multi-organ primary disease[e]

[a] Out of the 15 children (from 9 families) with BASD, 11 had 3beta-HSD deficiency, 3 had 5beta-reductase deficiency and 1 had Zellweger spectrum disorder.

[b] Defined as complete resolution of cholestasis and/or liver dysfunction and survival with native liver. There were no numerical data reported for cholestasis. The definition and reporting of liver dysfunction was unclear in the paper.

[c] 1 child with 3beta-HSD deficiency, started cholic acid treatment at age 6 months and died at age 9 months and the other child had 5beta-reductase deficiency and started cholic acid treatment at age 3 months and died at age 4 months.

[d] Diagnosed with 5beta-reductase deficiency, started cholic acid treatment at age 2 months and died at 4 months

[e] Diagnosed with Zellweger spectrum disorder, started cholic acid treatment at age 3.5 months and died at age 3 years

Abbreviations

3beta-HSD, 3-beta-hydroxy-delta5-C27-steroid oxidoreductase; 5beta-reductase, delta4-3--oxosteroid-5-beta reductase; BASD, bile acid synthesis disorders; LFTs, liver function tests

Table 11 Gonzales et al. 2009

	Presentation at start of cholic acid[a] treatment	**Presentation during cholic acid[a] treatment**
N	**15[b]**	**15[b]**
Clinical features	Hepatomegaly, n=15 Icteric, n=9 Splenomegaly, n=4 Signs of steatorrhoea, n=13 Areflexia, n=7 Jaundice, n=6	After 5 years of treatment: 'Normal' features reported, n=8 Hepatomegaly, n=4 Areflexia, n=3 Steatorrhoea reported to resolve in 9 children (p<0.005) At last visit[c]: 'Normal' features reported, n=10 Hepatomegaly, n=1 Areflexia, n=4

Growth	N/a	Growth in weight and height improved from means of −0.25 SD and −0.50 SD, respectively, up to a mean of +1 SD for both[d]
Abdominal ultrasonography findings	Gallstones, n=2 Hepatosplenomegaly, n=5 Hepatomegaly, n=9 Renal cysts, n=5 Ascites, n=1	After 5 years of treatment: 'Normal' findings reported, n=13 Hepatic dysmorphy, splenomegaly, n=1 Gallstones, n=1 At last visit[c]: 'Normal' findings reported, n=11 Hepatic dysmorphy, splenomegaly, n=1 Gallstones, n=3
Liver biochemistries	Abnormal total serum bilirubin, n=12 Abnormal serum ALT, n=11 Abnormal prothrombin time after vitamin K administration, n=7 Severe liver dysfunction (prothrombin time and clotting factor V <60%), n=3 Evaluation for liver transplantation because of decompensated liver disease or death of a previous sibling with similar liver disease, n=4. All patients had normal serum GGT activity as well as normal or low serum total bile acid concentration measured by routine assay (normal, <10micromoles/L)	Liver biochemistry test results were reported to be normalised in all patients and remained normal at follow-up (p< 0.0001 for total bilirubin and ALT levels, after 5 years cholic acid treatment) Serum alpha-fetoprotein level was normal during follow-up. Serum vitamin E concentration was reduced in all but 1 patient at presentation and normalised with cholic acid; it remained normal with cholic acid therapy after vitamin E supplements were stopped
Urinary bile acids[e]	Initially reported to be high in all patients	In patients with 3beta-HSD deficiency (n=13) there was a significant decrease in total urinary bile acids and in 3beta-hydroxylated-delta5[f] bile acids after 5 years of treatment and at last visit[c] (p<0.005 for both times) In patients with 5beta-reductase deficiency (n=2) there was a decrease in total urinary bile acids and in delta4-3-oxo[g] bile acids with cholic acid treatment after 5 years of treatment and at last visit[c]. However, with cholic acid and ursodeoxycholic acid treatment there was some improvement, but optimal suppression of synthesis of

		metabolites was not achieved.
Liver histology	Patients with 3beta-HSD deficiency: Severe cholestasis, n=12 Giant cell transformation n=7 Marked lobular (centrilobular and/or perisinusoidal) fibrosis, n=12 Septal portal fibrosis, n=11 (severe presentation, n=10) Patients with 5beta-reductase deficiency: Severe inflammation together with intense cholestasis and marked fibrosis, n=2	Patients with 3beta HSD deficiency[h]: Cholestasis resolved[i] Numbers for giant cell transformation, lobular fibrosis and septal portal fibrosis not reported Patients with 5beta-reductase deficiency: After 14 months of combined cholic acid and ursodeoxycholic acid treatment, fibrosis progressed or stabilised, although there was a decrease in inflammatory activity and cholestasis
Tolerance	• Compliance, based on urinary bile acid analyses, and tolerance were reported to be 'excellent' in all patients. • No serious adverse events were observed with a cumulative duration of treatment of more than 180 patient-years • Signs of cholic acid overdose were observed in 4 patients - clinical features of toxicity included pruritus, diarrhoea, and elevation of serum GGT and ALT activities and of total serum bile acid concentration (50 micromol/L). Liver biochemistry results returned to normal after reducing cholic acid dose • Four normal pregnancies in 2 patients resulted in the birth of 4 healthy infants while patients were treated with cholic acid	

[a] After initial treatment, the doses of cholic acid were adjusted individually based on the results of the follow-up urinary bile acid analyses by mass spectrometry and serum liver biochemistries. Doses for the different deficiencies were reported to be 14.2 mg/kg and 10 mg/kg in 3beta-HSD and 5beta-reductase deficiencies, respectively

[b] 8 patients initially received oral ursodeoxycholic acid as monotherapy before diagnosis of a BASD was established. These patients received treatment with ursodeoxycholic acid for the first 6 to 14 months of treatment with cholic acid to allow tapering of ursodeoxycholic acid

[c] Median follow-up with treatment was 12.4 years (range 5.6 to 15 years)

[d] Time period of change not stated in the study

[e] Total urinary bile acids represent the sum of atypical bile acids and physiologic bile acids.

[f] Atypical metabolite specific to 3beta-HSD deficiency

[g] Atypical metabolite specific to 5beta-reductase deficiency

[h] Mean follow-up of 6.2 years (range, 5.1 to 11.5 years)

[i] Mild ductular proliferation indicating biliary metaplasia of hepatocytes persisted in 4 patients

Abbreviations

3beta-HSD, 3-beta-hydroxy-delta5-C27-steroid oxidoreductase; 5beta-reductase, delta4-3--oxosteroid-5-beta reductase; ALT, alanine aminotransferase; GGT, gamma-

glutamyltransferase; SD, standard deviation

Appendix 5 Grading of the evidence base

Each study is assigned one of the following codes:

NSF-LTC Categories of research design

Primary research based evidence
P1 Primary research using quantitative approaches
P2 Primary research using qualitative approaches
P3 Primary research using mixed approaches (quantitative and qualitative)
Secondary research based evidence
S1 Meta-analysis of existing data analysis
S2 Secondary analysis of existing data
Review based evidence
R1 Systematic reviews of existing research

For each key outcome, studies were grouped and the following criteria were applied to achieve an overall grade of evidence by outcome.

Grade	Criteria
Grade A	More than 1 study of at least 7/10 quality and at least 1 study directly applicable
Grade B	One study of at least 7/10 which is directly applicable OR More than one study of a least 7/10 which are indirectly applicable OR More than one study 4-6/10 and at least one is directly applicable OR One study 4-6/10 which is directly applicable and one study of least 7/10 which is indirectly applicable
Grade C	One study of 4-6/10 and directly applicable OR Studies 2-3/10 quality OR Studies of indirect applicability and no more than one study is 7/10 quality

Applicability should be classified as:

- Direct studies that focus on people with the indication and characteristics of interest.

- Indirect studies based on evidence extrapolated from populations with other conditions and characteristics.