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Clinical evidence review of chenodeoxycholic acid for treating cerebrotendinous xanthomatosis

NHS England unique reference number URN 1623 / NICE ID004

First published: [Month year]

Updated: [Month year – delete if not applicable]

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 chenodeoxycholic acid (proprietary name 'Chenodeoxycholic Acid Leadiant') for treating inborn errors of primary bile acid synthesis caused by sterol 27-hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis [CTX]) in people aged 1 month and over.

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). CTX is an inborn error of primary bile acid synthesis that results in deficiency of the sterol 27-hydroxylase enzyme, preventing cholesterol from being converted to chenodeoxycholic acid. This leads to deposits of cholesterol and cholestanol (a derivative of cholesterol) in nerve cells and membranes, which can damage the brain, spinal cord, tendons, lens of the eye and arteries. People with CTX may die prematurely because of progressive neurological deterioration.

The evidence review primarily considers the results of 2 small retrospective cohort studies (n=35 and n=28) that were considered by the European Medicines Agency during the regulatory process for the authorisation of chenodeoxycholic acid (see the European public assessment report). It also includes a smaller study by del Mar Amador et al. (2018) (n=14) and outlines a literature review included in the European public assessment report (39 case series and 31 single case reports, n=204).

Effectiveness

In people with CTX who were treated with chenodeoxycholic acid in the main retrospective study (CDCA-STUK-15-001, n=35, mean duration of treatment 10.74 years), there were statistically significant improvements in mean serum cholestanol and urinary bile alcohol levels. Statistically significant improvements in mean serum cholestanol levels were also seen in people who were treated with chenodeoxycholic acid in the second, supportive retrospective study considered by the European Medicines Agency (CDCA-STRCH-CR-14-001, n=28, median follow-up 5.75 years) and the study by del Mar Amador et al. (n=14, mean follow-up 5 years). The reduction in the build-up of these substances suggests that

replacement treatment with chenodeoxycholic acid may restore the normal production of bile acids.

Neurological disability and dependence was measured using 2 scales (the Rankin Scale and the Expanded Disability Status Scale [EDSS]) in the 2 larger studies. In the main study (CDCA-STUK-15-001), scores on both scales remained stable or improved between baseline and the most recent clinical current visit in about 80% of people. In the supportive study (CDCA-STRCH-CR-14-001), scores remained stable in about 60% of people when the Rankin scale was used and about 50% of people when the EDSS was used. Overall, there was a statistically significant worsening of the mean Rankin and EDSS scores from baseline in the supportive study, but not in the main study. The study by del Mar Amador et al. also considered EDSS scores. It found that, overall, mean scores remained stable.

Generally, signs and symptoms of CTX resolved, improved or remained stable (not defined) in most people over the course of the main study (CDCA-STUK-15-001). For example, diarrhoea resolved in everyone who had this symptom at baseline and cognitive impairment resolved, improved or remained stable in everyone with this symptom. In the supportive study (CDCA-STRCH-CR-14-001), signs and symptoms of the disease remained stable in most people, although fewer people saw positive outcomes than in the main study and some deteriorated. The poorer outcomes in the supportive study may be because people in this study were, on average, older and had higher disability scores at baseline.

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

In summary, the studies suggest that replacement therapy with chenodeoxycholic acid may normalise the results of certain laboratory tests, and may improve or, more often, stabilise symptoms of CTX, particularly in younger people with lower disability scores. When interpreting these results, the evidence gaps and limitations (see below) should also be taken into account.

Safety and tolerability

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

In the main study (CDCA-STUK-15-001), only 3 treatment-related adverse events were seen. These were constipation in 2 people and toxic hepatitis in 1 person, which were not considered to be serious. No treatment-related adverse events were seen in the supportive study (CDCA-STRCH-CR-14-001), and treatment was reported to be 'well tolerated' in people in the study by del Mar Amador et al.

Evidence gaps and limitations

There have been no prospective, controlled clinical studies of chenodeoxycholic acid in CTX and the rarity of the condition makes higher quality studies difficult. The studies included in the evidence review are small (n=35, n=28 and n=14), uncontrolled, retrospective studies, therefore their results should be interpreted with caution. The timing of post treatment and most recent clinical visits is unclear from the European public assessment report. Data were commonly missing across the time points, and most outcomes in the 2 larger studies were reported as improved, stabilised or deteriorated, but these are not defined. Also, many people received additional treatments as well as chenodeoxycholic acid, which may disguise the true effect of chenodeoxycholic acid. The studies' design and conduct mean they are subject to bias and confounding, are difficult to interpret, and cannot support firm conclusions.

Only limited data are available for children, no data are available for people with renal or hepatic impairment, and there are no or limited data on using chenodeoxycholic acid in pregnant women (summary of product characteristics).

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Abbreviations

Term	Definition
CTX	Cerebrotendinous xanthomatosis (a rare genetic disorder in which an enzyme deficiency prevents cholesterol from being converted to chenodeoxycholic acid
EDSS	Expanded Disability Status Scale (a tool used to rate a person's level of disability)
EPAR	European public assessment report (which explains how a medicine, such as chenodeoxycholic acid, was assessed for a license in the EU, and how it may be used)
SARA	Scale for the Assessment and Rating of Ataxia (a tool to used assess and rate a person's level of control of bodily movements)

Medical definitions

Term	Definition
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)
Bile alcohols	Bile alcohols are substances that are removed from the body in urine. Urinary bile alcohol levels are higher than normal in people with CTX
Cataracts	Clouding of the lens of the eye affecting vision
Cerebrotendinous xanthomatosis (CTX)	A rare genetic disorder in which an enzyme deficiency (sterol 27-hydroxylase deficiency) prevents cholesterol from being converted to chenodeoxycholic acid
Chenodeoxycholic acid	A bile 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
Cognitive impairment	This is when a person has trouble remembering, learning new things, concentrating or making decisions that affect their everyday life
Expanded Disability Status Scale (EDSS)	A tool used to rate a person's level of disability
Enzyme	A protein that helps to produce a chemical reaction in the body
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 are usually broken down by enzymes
Jaundice	Yellowing of the skin, mucous membranes and whites of the eyes
Neurological	Relating to the nerves and the nervous

	system in the body
Psychiatric	Relating to mental illness (such as anxiety or depression) or its treatment
Rankin Scale	A tool used to rate a person's level of disability and dependence
Sterol 27-hydroxylase	An enzyme deficiency of which can cause CTX
Xanthomas	Benign fatty tumours or lumps caused by deposits of fats or lipids, such as cholesterol

1 Introduction

Disease background

1.1 Cerebrotendinous xanthomatosis (CTX) is 1 of a number of inborn errors of primary bile acid synthesis. These disorders are rare genetic conditions caused by mutations in specific genes that are passed down to a child from each parent (autosomal recessive inheritance). The genetic mutations lead to deficiencies in enzymes that are needed for the liver to convert cholesterol in the body to bile acids (primarily cholic acid and chenodeoxycholic acid) via a complex series of chemical reactions. This results in accumulation of abnormal bile acids, intermediary metabolites (other substances that would usually be broken down) and cholesterol in the body, which can damage certain organ systems (National Organization for Rare Disorders: Bile acid synthesis disorders).

1.2 The age of onset, specific symptoms, and rate of progression varies significantly from 1 person to another depending, in part, on the specific underlying enzyme defect causing the bile acid synthesis disorder. The main symptom of most inborn errors of primary bile acid synthesis is interruption or suppression of the flow of bile from the liver (cholestasis) and malabsorption of fat-soluble vitamins. Signs of cholestasis include jaundice (yellowing of the skin, mucous membranes and whites of the eyes) and problems with growth (National Organization for Rare Disorders: Bile acid synthesis disorders).

1.3 CTX results in deficiency of the sterol 27-hydroxylase enzyme and generally produces different symptoms from other inborn errors of primary bile acid synthesis. The sterol 27-hydroxylase enzyme deficiency prevents cholesterol from being converted to chenodeoxycholic acid. This leads to deposits of cholesterol and cholestanol (a derivative of cholesterol) in nerve cells and membranes, which can damage the brain, spinal cord, tendons, lens of the eye and arteries (National Organization for Rare Disorders: Cerebrotendinous xanthomatosis).

1.4 People with CTX commonly experience diarrhoea and cataracts (clouding of the lens of the eye) in childhood and may develop benign xanthomas (fatty tumours) of the tendons during adolescence. If CTX is not treated, it can cause progressive neurologic problems in young adulthood, such as seizures, ataxia (loss of control of bodily movements), cognitive impairment and dementia. Cardiovascular disease, hypothyroidism and osteoporosis have been reported in people with CTX (National Organization for Rare Disorders: Cerebrotendinous xanthomatosis).

1.5 The mean age of diagnosis has been reported as around 35–37 years, by which time there is often significant neurological involvement. Some people with symptoms of CTX in adulthood previously experienced cholestatic jaundice during infancy (National Organization for Rare Disorders: Cerebrotendinous xanthomatosis).

1.6 The symptoms and progression of CTX vary considerably from 1 person to another, even in twins with the same genetic mutation. People with CTX may die prematurely because of progressive neurological deterioration (National Organization for Rare Disorders: Cerebrotendinous xanthomatosis).

1.7 Oral bile acid replacement therapy is used to stop the progression of CTX or prevent symptoms from occurring in asymptomatic individuals. People with CTX who started treatment after the age of 25 years have shown worse outcomes, with more limited ambulation and cognitive impairment than those who started treatment before the age of 25 years. Therefore, early diagnosis is important to prevent disease complications (National Organization for Rare Disorders: Cerebrotendinous xanthomatosis).

Focus of review

1.8 In line with the marketing authorisation, the focus of this review is on chenodeoxycholic acid (proprietary name, ‘Chenodeoxycholic Acid Leadiant’).

1.9 Chenodeoxycholic acid is indicated for treating inborn errors of primary bile acid synthesis caused by sterol 27-hydroxylase deficiency (presenting as CTX) in infants, children and young people aged 1 month to 18 years and adults.

Epidemiology and needs assessment

1.10 Recent estimates for the incidence of CTX range from about 1:135,000 to 1:460,000 in people of European family origin and about 1 in 70,000 in people of Asian family origin. However, only around 300 people with CTX have been described worldwide (National Organization for Rare Disorders: Cerebrotendinous xanthomatosis).

1.11 A bibliographic study of the epidemiology of rare diseases estimated that there are about 200 people in Europe with CTX (EURODIS and ORPHANET: Rare diseases in numbers). The company for chenodeoxycholic acid estimates that there are 24 people with CTX in England who would be eligible for treatment, 5 of whom are children.

Product overview

Mode of action

1.12 This treatment is used to replace the chenodeoxycholic acid that is not produced in people with CTX because of the enzyme deficiency. Chenodeoxycholic acid therapy reduces production of atypical bile alcohols and bile acids, cholesterol and cholestanol (summary of product characteristics).

Regulatory status

1.13 Chenodeoxycholic acid received a marketing authorisation in May 2017 for treating inborn errors of primary bile acid synthesis caused by sterol 27-hydroxylase deficiency (presenting as CTX) in infants, children and young people aged 1 month to 18 years and adults.

Dosing information

1.14 Each capsule contains 250 mg of chenodeoxycholic acid.

1.15 For adults, the starting dosage is 750 mg/day in 3 divided doses. The daily dose can be increased to a maximum of 1000 mg/day if serum cholestanol or urinary bile alcohols remain elevated (summary of product characteristics).

1.16 For children and young people aged 1 month to 18 years, the starting dosage is 5 mg/kg/day in 3 divided doses. Where the dose calculated is not a multiple of 250 mg, the nearest dose below the maximum dosage of 15 mg/kg/day should be selected (summary of product characteristics).

1.17 For infants and children who cannot swallow capsules, chenodeoxycholic acid capsules may be opened and the contents added to sodium bicarbonate solution 8.4% to produce a suspension (summary of product characteristics).

1.18 Please see the summary of product characteristics for full dosing information.

Treatment pathway and current practice

1.19 There are no published, agreed, UK-based treatment pathways for treating inborn errors of bile acid synthesis. Chenodeoxycholic acid has been used as an off-label treatment for CTX for around 20 years. Ataxia UK (the only UK body to publish guidance on the management of CTX) recommends prompt diagnosis and treatment of CTX with chenodeoxycholic acid.

1.20 The Orphanet (a European consortium of 40 countries, including the UK, that gathers information on rare diseases) monograph for cerebrotendinous xanthomatosis states first-line treatment is chenodeoxycholic acid, which normalises bile acid synthesis and cholestanol concentrations.

1.21 Cholic acid has been used as an alternative to chenodeoxycholic acid. The Orphanet monograph states that it 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 (hepatotoxicity) sometimes associated with chenodeoxycholic acid. However, no evidence to support this statement is provided.

1.22 Ursodeoxycholic acid was used for treating but CTX in the past, but was shown to be ineffective (Berginer VM et al. 1984, Koopman BJ et al. 1988 and Waterreus RJ et al. 1987). Please also see section 2.37.

1.23 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 292 references (see appendix 1 for search strategy). These references were screened using their titles and abstracts and 15 full text references were obtained and assessed for relevance. Full text inclusion and exclusion criteria were applied to the identified studies and none were included in the clinical evidence review (see appendix 2 for inclusion criteria and a list of studies excluded at full text with reasons).

2.2 Two retrospective cohort studies that were considered by the European Medicines Agency during the regulatory process were included in this evidence review. These studies were described in the European public assessment report but have not currently been published in a peer reviewed journal and, therefore, were not identified by the searches. A literature review was also included in the European public assessment report and has been outlined in this evidence review. In addition, a study was published in March 2018 (del Mar Amador M et al. 2018), after the searches were undertaken, and has been included.

2.3 The company submission highlighted the 2 studies that were described in the European public assessment report.

Overview of included studies

2.4 A summary of the 3 retrospective studies that are discussed in this evidence review is shown in table 1 (see evidence tables for full details).

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Main outcomes[1]
CDCA-STUK-15-001 Main study (Retrospective cohort study in 1 centre in the Netherlands)	People with CTX for at least 1 year (n=35; mean duration of treatment 10.74 years; age between 2 and 75 years [at the first treatment, 15 people were aged <21 years and 20 were aged ≥21 years]) It is not known how many people were asymptomatic at baseline, but most people had at least 1 symptom[2]	Chenodeoxycholic acid 750 mg/day or 15 mg/kg/day (No comparator) Some people were taking other treatments for CTX, but the number of people and type of treatment were not clearly reported	Serum levels of cholestanol and urinary bile alcohols Disease progression[3] Adverse events
CDCA-STRCH-CR-14-001 Supportive study (Retrospective cohort study in 1 centre in Italy)	People with CTX for at least 1 year (n=28, median follow-up 5.75 years; age between 2 and 75 years [average age not reported]) It is not known how many people were asymptomatic at baseline, but most people had 1 or more symptoms[2] It is not known how many people	Chenodeoxycholic acid 750 mg/day (No comparator) Some people were taking other treatments for CTX, but the number of people and type of treatment were not clearly reported	Serum levels of cholestanol Disease progression[3] Adverse events

	were asymptomatic at baseline, but most people had 1 or more symptoms[2]		
del Mar Amador M et al. 2018 (Retrospective case series in 1 centre in France)	People with CTX (n=14, mean follow-up 5 years; mean age 29 years) All cases had at least 1 symptom	Chenodeoxycholic acid Dosage not reported (No comparator) It is not known how many people were using other treatments for CTX	Serum levels of cholestanol Disease progression[3] Changes in brain structure (n=4)
[1] On-treatment assessments were compared to assessments at baseline. In the first 2 studies, data were collected from the beginning of treatment up to 2 years after (with a minimum of 1 year) and at the most recent clinical visit [2] For example, in the main and supportive studies respectively, 74% and 54% of people had diarrhoea, 65% and 77% had neurological impairment and 58% and 77% had cognitive impairment. [3] Disease progression was measured using a range of parameters including disability scores, laboratory parameters and disease signs and symptoms			
Abbreviations: CTX, Cerebrotendinous xanthomatosis			

2.5 Seventy articles were included in the literature review in the European public assessment report. Of these, 39 were case series and 31 were single case reports. Data for 204 people was included in the overall efficacy summary. In some cases, other treatments were added to chenodeoxycholic acid or separately tested such as ursodeoxycholic acid, simvastatin, pravastatin and LDL-apheresis. Age at the start of treatment varied between 2 months and 64 years, and follow-up ranged from 1 month to 18 years. The usual adult dosage was 750 mg per day or 15 mg/kg three times daily; however, lower doses such as 300 mg/day were also used. Response was measured in various ways including biochemical and clinical outcomes.

Key outcomes

2.6 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.

Effectiveness

2.7 **Serum cholestanol:** cholestanol is a substance in the body that is derived from cholesterol, which can accumulate in people with CTX, causing symptoms (see disease background section). Treatment with chenodeoxycholic acid aims to replace the missing bile acid so that cholesterol and cholestanol can be broken down.

2.8 In study CDCA-STUK-15-001, people had raised serum cholestanol levels at baseline. After chenodeoxycholic acid treatment, where data were available, statistically significant reductions in mean levels were seen at all time points compared with baseline ($p<0.001$ at post treatment visit 1 [n=23], post treatment visit 2 [n=25] and the most recent clinical visit [n=23]). The timing of these visits is unclear from the European public assessment report. Chenodeoxycholic acid treatment was also associated with statistically significant decreases in mean serum levels of cholestanol from baseline at all time points in study CDCA-STRCH-CR-14-001 ($p<0.001$ at post treatment visit 1 [n=23], post treatment visit 2 [n=19] and the most recent clinical visit [n=22]).

2.9 Serum cholestanol levels were raised at baseline in all 14 people in the study by del Mar Amador et al. The authors of the paper state that levels became normal in all participants within a few months of starting treatment with chenodeoxycholic acid ($p<0.001$).

2.10 **Urinary bile alcohol**: bile alcohols are substances that are removed from the body in urine. Urinary bile alcohol levels are higher than normal in people with CTX. Treatment with bile acids, such as chenodeoxycholic acid, can reduce levels.

2.11 All people in study CDCA-STUK-15-001 had raised urinary bile alcohol levels at baseline. Data were missing for 25% of cases; however, where data were available, improvements were usually seen after chenodeoxycholic acid treatment. A total of 86% (18/21), 100% (19/19) and 79% (11/14) of people had improved urinary bile alcohol levels at post treatment visit 1, post treatment visit 2 and the most recent clinical visit

respectively (all statistically significant compared with baseline, p<0.001). In about 10% of cases, urinary bile alcohol levels remained high. Urinary bile alcohol levels were not reported for study CDCA-STRCH-CR-14-001.

2.12 In the literature review in the European public assessment report, biochemical data were available for 174 people and a response was seen in everyone (100%) after chenodeoxycholic acid treatment. Individual biochemical tests were not reported.

2.13 **Diarrhoea**: 74% (23/31) of people in study CDCA-STUK-15-001 had diarrhoea at baseline, which resolved in all cases by the most recent clinical visit. In study CDCA-STRCH-CR-14-001, diarrhoea did not resolve in all cases. At baseline, 54% (14/26) of people had diarrhoea, and 42% (11/26) of cases in this study had diarrhoea at the most recent clinical visit.

2.14 Diarrhoea was reported in 8% (17/204) of people in the literature review in the European public assessment report. It resolved in 16 of these (94%) with chenodeoxycholic acid treatment. Diarrhoea was not assessed in the study by del Mar Amador et al.

2.15 **Xanthomas**: these fatty tumours were seen in 8/31 (26%) of people at baseline and 10/31 people (32%) at the most recent clinical visit in study CDCA-STUK-15-001. It is not reported whether xanthomas improved, stabilised or deteriorated. Of the 21/26 people (81%) who had xanthomas at baseline in study CDCA-STRCH-CR-14-001, these were stable in 15 people (71%) and had deteriorated in 6 people (29%) at the most recent clinical visit.

2.16 Outcomes for xanthomas were not reported for the literature review in the European public assessment report or the study by del Mar Amador et al.

2.17 **Cataracts**: an improvement in the number of people with cataracts was seen in study CDCA-STUK-15-001 (from 20/31 people [65%] to 0/31 people). However, this was because cataracts were surgically removed; it was not a result of chenodeoxycholic acid treatment. In

23/26 people who had cataracts at baseline in study CDCA-STRCH-CR-14-001, cataracts were stable in 22 people and deteriorated in 1 person at the most recent clinical visit.

2.18 In the study by del Mar Amador et al., although this outcome was not formally assessed, 11/14 people (79%) reportedly had cataract surgery. Outcomes for cataracts were not reported for the literature review in the European public assessment report.

2.19 **Cognitive impairment**: in study CDCA-STUK-15-001, 18/31 people (58%) had cognitive impairment (not defined) at baseline. This had reduced to 16 people at the most recent clinical visit, of whom 1 person (6%) had improved and 15 (94%) were stable. In study CDCA-STRCH-CR-14-001, 20 people at baseline compared with 22/26 people (85%) at the most recent clinical visit had cognitive impairment, which was stable in 16 (73%) and had deteriorated in 6 (27%).

2.20 Cognitive impairment was reported in 35/204 people (17%) in the literature review in the European public assessment report. Of these, 31 people stabilised or improved with chenodeoxycholic acid treatment (89%). Continued deterioration was reported in 4 people (11%). Outcomes for cognitive impairment were not reported in the study by del Mar Amador et al.

2.21 **Psychiatric impairment**: 6/31 people (19%) had psychiatric impairment (not defined) at baseline in study CDCA-STUK-15-001, which resolved, improved or stabilised in all 6. Of 5 people who had psychiatric impairment at the most recent clinical visit, 1 had improved and 4 were stable. Signs deteriorated in 1 person who did not have symptoms at baseline. In study CDCA-STRCH-CR-14-001, 13/26 people (50%) had psychiatric impairment at baseline. This was stable in 12 cases (92%) and had deteriorated in 1 case (7%) at the most recent clinical visit.

2.22 Outcomes for psychiatric impairment were not reported for the literature review in the European public assessment report or the study by del Mar Amador et al.

2.23 **Neurological impairment and disability**: at baseline in study CDCA-STUK-15-001, 20/31 people (65%) had neurological impairment. This reduced to 17/31 people (55%) at the most recent clinical visit. Polyneuropathy, pyramidal dysfunction and cerebellar dysfunction (types of neurological impairment) stabilised or improved in 11/11 people (100%), 9/15 people (60%) and 12/14 people (86%) respectively.

2.24 Neurological disability was assessed in the studies using Rankin scale and Expanded Disability Status Scale (EDSS) scores. In study CDCA-STUK-15-001, Rankin scale scores improved in 4/26 people (15%), stabilised in 18/26 people (69%) and deteriorated in 4/26 people (15%). EDSS scores improved in 6/26 people (23%), stabilised in 14/26 people (54%) and deteriorated in 6/26 people (23%). Overall, mean Rankin scale and EDSS scores deteriorated by a small amount between baseline and the most recent clinical visit. However, these changes were not statistically significant.

2.25 In study CDCA-STRCH-CR-14-001, 20/26 people (77%) had neurological impairment at baseline. This number was unchanged at the final clinical visit, where impairment remained stable in 9 people and had deteriorated in 11 people. In this study, Rankin and EDSS scores remained stable in 62% and 50% of people respectively. However, overall, there were statistically significant deteriorations in mean Rankin and EDSS scores between baseline and the most recent clinical visits ($p=0.001$ and $p<0.001$ respectively).

2.26 Overall, mean EDSS scores remained stable after chenodeoxycholic acid treatment in the study by del Mar Amador et al. EDSS scores improved in 4 patients (28.6%), remained stable in 5 patients (35.7%) and worsened in 5 patients (35.7%). The 3 people whose EDSS score worsened by at least 1 point had the longest time between experiencing their first cognitive

and/or motor symptoms and starting treatment (25–32 years). In this study neuropathy was also assessed using electroneuromyography, which measures nerve conduction. Statistically significant improvements were seen with chenodeoxycholic acid treatment.

2.27 In the literature review in the European public assessment report, neurological impairment was reported in 97 people. After treatment with chenodeoxycholic acid, 71 people stabilised or improved (73%) and 26 people deteriorated (27%).

2.28 **Grade of evidence**: the grade of evidence for the majority of the outcomes is B because (apart from urinary bile alcohol, which is based on 1 study and graded C) the evidence is based on 2 or 3 studies scoring 4–6 points, which are directly applicable to people with the indication of interest.

2.29 **Limitations**: key limitations include the small numbers of cases in the studies, the retrospective design of the studies and the lack of comparators. In the 2 main studies, data were commonly missing across the time points, and many people received additional treatments as well as chenodeoxycholic acid. Most outcomes were reported as improved, stabilised or deteriorated but these are not defined, and few statistical analyses were undertaken.

Safety and tolerability

2.30 In study CDCA-STUK-15-001, 76 adverse events were reported in 26/35 people (74.3%). Nine of these events in 7 people were considered to be serious. There were 16 adverse events in 9/28 people (32.1%) in study CDCA-STRCH-CR-14-001, which were all considered to be serious.

2.31 Three adverse events in study CDCA-STUK-15-001 were considered to be related to chenodeoxycholic acid treatment. These were constipation in 2 people and toxic hepatitis in 1 person, which were not thought to be serious. No adverse events were considered to be treatment-related in study CDCA-STRCH-CR-14-001.

2.32 Treatment was reported to be 'well tolerated' in people in the study by del Mar Amador et al. No further details were given in the paper.

2.33 In the literature review included in the European public assessment report, only 1 relevant article describing an adverse event with chenodeoxycholic acid was identified. This single case of suspected toxic hepatitis was also recorded in study CDCA-STUK-15-001.

2.34 According to the European public assessment report, 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 chenodeoxycholic acid in the studies were generally not serious and mostly related to the underlying disease condition.

Evidence gaps and limitations

2.35 There have been no prospective controlled clinical studies of chenodeoxycholic acid in CTX. The rarity of the condition makes such studies unfeasible, for example, because they would need to involve many centres and have a long follow-up period. No dose-response studies have been undertaken, and the optimal dosage of chenodeoxycholic acid for CTX is unclear; however, it has been used in clinical practice for 40 years. The usual dosage (750 mg per day in adults and 15 mg/kg/day in children) was chosen by clinicians based on the dosage of chenodeoxycholic acid for gallstone dissolution (European public assessment report), and this is the dosage that was used in the studies, and which has been licensed based on the available evidence.

2.36 This evidence review includes data on the efficacy and safety of chenodeoxycholic acid for CTX from 3 retrospective studies undertaken in 3 centres in Europe. The main limitations of the studies include their small size (n=35, n=28 and n=14, therefore, limited data are available for clinical efficacy and safety), lack of control groups (therefore, no comparative data are available to show if chenodeoxycholic acid works better than placebo or an active treatment), and their retrospective nature (therefore,

they are subject to bias and confounding). The European public assessment report notes that all efficacy outcomes in the main and supportive study had a considerable amount of missing data and that results should be interpreted with caution. The report also notes that it is likely that the clinical effects of chenodeoxycholic acid may be overestimated because multiple therapies (dietary, pharmaceutical and supportive) are used in people with CTX.

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

2.38 Outcomes in the main and supportive cohort studies were reported at post treatment visit 1, post treatment visit 2 and the most recent clinical visit. However, it is not reported when these visits occurred, on average or as a range. Also, outcomes were reported as improved, stabilised or deteriorated but these are not defined. For example, it is not known whether improvement is a numerical improvement, a statistically significant improvement or a clinical improvement based on a minimum clinically important difference.

2.39 The mean age of the patient population in study CDCA-STUK-15-001 was younger than the population in study CDCA-STRCH-CR-14-001 (26 years compared with 35 years). This was reflected in the level of disability in the

2 study cohorts before treatment was started, with the population in study CDCA-STRCH-CR-14-001 having a higher disability score at (European public assessment report). This may account for differences in treatment outcomes between the studies.

2.40 The European public assessment report noted that late detection of symptoms of CTX in people in the studies led to irreversible damage, especially of the nervous system and connective tissue, which could not be corrected by further therapy. Nevertheless, the European public assessment report considered that a demonstrable decrease in morbidity was found for neurological symptoms after chenodeoxycholic acid treatment was started.

2.41 The Rankin scale and EDSS were used to assess neurological disability in the studies. These scales have not been validated in CTX and no scales are available specifically for this condition. Nevertheless, the European public assessment report considers that use of the Rankin scale and EDSS is appropriate for CTX.

2.42 Many of the limitations above also apply to the smaller study by del Mar Amador et al. The study is retrospective, included only 14 people and does not have a control group. Therefore, the data is subject to bias and confounding and cannot support firm conclusions. Some of the conclusions in the paper are based on small subgroups of people in the study (for example, ataxia scores and brain imaging). All MRI scans were acquired during routine clinical follow-up, which sometimes resulted in a lower quality image compared with research MRI. It is unclear whether statistically significant results are clinically important.

2.43 The systematic review of published literature that was discussed in the European public assessment report was limited to articles published in English. Reporting and publication bias are potential concerns given the small number of cases reported in the literature as well as their geographic concentration. Only limited information on outcomes is provided in the report.

2.44 According to the summary of product characteristics, only limited data are available for children. In the 2 studies, only 14 children and young people were treated with chenodeoxycholic acid: 1 infant aged less than 2 years, 6 children aged 2 to less than 12 years, and 7 young people aged 12 to less than 18 years.

2.45 No data are available for people with renal or hepatic impairment and they should be carefully monitored and the dose titrated individually. There are no or limited data on using chenodeoxycholic acid in pregnant women. Studies in animals have shown reproductive toxicity. Chenodeoxycholic acid is not recommended during pregnancy and women of childbearing potential should use an effective method of contraception (but not an oral contraceptive; summary of product characteristics).

Table 2 Grade of evidence for key outcomes

Outcome measure	Study	Critical appraisal score	Applicability	Grade of evidence	Interpretation of evidence
Serum cholestanol levels	CDCA-STUK-15-001	5/10	Directly applicable	B	Cholestanol is a substance in the body, which can build up in people with CTX and damage organs. This outcome compared average levels of blood cholestanol before and after chenodeoxycholic acid to see if treatment reduced the levels. CDCA-STUK-15-001 found a statistically significant reduction at 3 different time points compared with pre-treatment levels. At the most recent clinical visit (an average of about 10 years' after treatment), cholestanol reduced by 63 micromol/litre compared with baseline (down from 72 to 9 micromol/litre). There is a 95% probability that the true reduction is within the range of 46–80 micromol/litre. Similar results were seen in CDCA-STRCH-CR-14-001, the study by del Mar Amador and the literature review in the European public assessment report. In summary, results suggest chenodeoxycholic acid reduced serum levels of cholestanol. The results of the studies should be interpreted with caution because they are small (n=35, n=28 and n=14), uncontrolled, retrospective studies. In the 2 main studies, data were commonly missing across time points and many people received additional treatments as well as chenodeoxycholic acid, which may disguise the true treatment effect of chenodeoxycholic 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.
	CDCA-STRCH-CR-14-001	5/10	Directly applicable		
	Del Mar Amador et al. (2018)	4/10	Directly applicable		
Urinary bile alcohol levels	CDCA-STUK-15-001	5/10	Directly applicable	C	Bile alcohols are substances removed from the body in urine. Urinary bile alcohol levels are higher than normal in people with CTX, and are a marker of uncontrolled entry of cholesterol into the bile acid synthesis pathway. Chenodeoxycholic acid reduces this uncontrolled entry by inhibiting cholesterol 7alpha-hydroxylase. This outcome compared average levels of urinary bile alcohols before and after chenodeoxycholic acid to see if treatment reduced the amount. CDCA-STUK-15-001 found a statistically significant reduction in the amount of bile alcohols in people's urine at 3 different time points compared with pre-treatment levels. Urinary bile alcohol levels improved from baseline in 18/21 people (86%), 19/19 people (100%) and 11/14 people (79%) at post treatment visit 1, post

					treatment visit 2 and the most recent clinical visit respectively. In summary, urinary bile alcohol levels reduced in about 90% of people treated with chenodeoxycholic acid, suggesting improvement in one of the fundamental mechanisms underlying the disease. The results of CDCA-STUK-15-001 should be interpreted with caution because it is a small (n=35), uncontrolled, retrospective study. Data were commonly missing across the time points and many people received additional treatments as well as chenodeoxycholic acid, which may disguise the true treatment effect of chenodeoxycholic acid. The weaknesses in the design and conduct of the study mean it is subject to bias and confounding, is difficult to interpret and cannot support firm conclusions.
Diarrhoea	CDCA-STUK-15-001	5/10	Directly applicable	B	This outcome compared the number of people with diarrhoea before and after treatment. CDCA-STUK-15-001 found diarrhoea resolved by the most recent clinical visit in 23/23 people (100%) who had this symptom at baseline (23/31 people [74%]). Similar results were seen in the literature review in the European public assessment report, in which diarrhoea resolved in 16/17 (94.1%) of people. However, in CDCA-STRCH-CR-14-001, 11/26 people (42%) still had this diarrhoea at the most recent clinical visit. Note that people in CDCA-STRCH-CR-14-001 were, on average, older (mean age 35 years compared with 26 years in CDCA-STUK-15-001) and had higher disability scores at baseline. Results suggest that chenodeoxycholic acid may improve symptoms of diarrhoea, with the chances of success increasing in younger people, who were at an earlier stage of the disease. The results of the studies should be interpreted with caution because they are small (n=35 and n=28), uncontrolled, retrospective studies. Data were commonly missing across the time points and many people received additional treatments as well as chenodeoxycholic acid, which may disguise the true treatment effect of chenodeoxycholic 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.
	CDCA-STRCH-CR-14-001	5/10	Directly applicable		
Xanthomas	CDCA-STUK-15-001	5/10	Directly applicable	B	Xanthomas are benign fatty tumours or lumps caused by deposits of fats or lipids, such as cholesterol. This outcome compared the number of people with xanthomas before and after chenodeoxycholic acid to see if treatment reduced this symptom. CDCA-STUK-15-001 found that 8/31 people (26%) had xanthomas at baseline compared with 10/31 people (32%) at the most recent clinical visit. It is not reported
	CDCA-STRCH-	5/10	Directly applicable		

	CR-14-001				whether xanthomas improved, stabilised or deteriorated. CDCA-STRCH-CR-14-001 reported that xanthomas improved or stabilised in 15/21 people (71%) and worsened in 6/21 people (29%) who were taking chenodeoxycholic acid at the most recent clinical visit. Results suggest that chenodeoxycholic acid has no protective effect on the incidence of xanthomas, although it may help to improve or stabilise xanthomas in some people who currently have these. The results of the studies should be interpreted with caution because they are small (n=35 and n=28), uncontrolled, retrospective studies. Data were commonly missing across the time points and many people received additional treatments as well as chenodeoxycholic acid, which may disguise the true treatment effect of chenodeoxycholic acid. Outcomes were reported as improved, stabilised or deteriorated but these are not defined. 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.
Cataracts	CDCA-STUK-15-001	5/10	Directly applicable	B	Cataracts are clouding of the lens of the eye affecting vision. This outcome compared the number of people with cataracts before and after chenodeoxycholic acid to see if treatment reduced this symptom. In CDCA-STUK-15-001, cataracts resolved in 20/31 people (65%) by the most recent clinical visit. However, this was because cataracts were surgically removed and was not because of chenodeoxycholic acid treatment. In CDCA-STRCH-CR-14-001 cataracts remained stable in most people with these symptoms. In summary, there is not enough evidence to show a treatment effect for chenodeoxycholic acid on cataracts. The results of the studies should be interpreted with caution because they are small (n=35 and n=28), uncontrolled, retrospective studies. Data were commonly missing across the time points and many people received additional treatments as well as chenodeoxycholic acid, including cataract surgery, which means the true treatment effect of chenodeoxycholic acid is unclear. 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.
	CDCA-STRCH-CR-14-001	5/10	Directly applicable		
Cognitive impairment	CDCA-STUK-15-001	5/10	Directly applicable	B	Cognitive impairment is when a person has trouble remembering, learning new things, concentrating, or making decisions that affect their everyday life. This outcome compared the number of people with cognitive impairment before and after chenodeoxycholic acid to see if treatment reduced this symptom. In CDCA-STUK-15-001, 18/31 people (58%) had cognitive impairment at baseline.
	CDCA-STRCH-	5/10	Directly applicable		

	CR-14-001				This had reduced to 16 at the most recent clinical visit, of whom 1 person (6%) had improved and 15 (94%) were stable. Similar results were seen in the literature review in the European public assessment report. By contrast, in CDCA-STRCH-CR-14-001, 2 additional people had cognitive impairment by the most recent clinical visit and it got worse in about a quarter of people. In summary, cognitive impairment did not deteriorate in people taking chenodeoxycholic acid in CDCA-STUK-15-001, with a younger population (mean age 26 years) who were at an earlier stage of disease. By contrast, in CDCA-STRCH-CR-14-001, with the older population (mean age 35 years) with worse disability scores at baseline, cognitive impairment got worse in about a quarter of people by the most recent clinical visit and more people had it. The results of the studies should be interpreted with caution because they are small (n=35 and n=28), uncontrolled, retrospective studies. Data were commonly missing across the time points and many people received additional treatments as well as chenodeoxycholic acid, which may disguise the true treatment effect of chenodeoxycholic acid. Outcomes were reported as improved, stabilised or deteriorated but these are not defined. 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. Also, there is little information available about what the broad term 'cognitive impairment' includes.
Psychiatric impairment	CDCA-STUK-15-001	5/10	Directly applicable	B	Psychiatric impairment is mental illness. This outcome compared the number of people with psychiatric impairment before and after chenodeoxycholic acid to see if treatment reduced this symptom. In CDCA-STUK-15-001, 6/31 people (19%) had psychiatric impairment at baseline, which resolved, improved or stabilised in all 6. However, it deteriorated in 1 person who did not have these symptoms at baseline. Similar results were seen in CDCA-STRCH-CR-14-001 study in which only 1 person got worse on treatment but none improved. In summary, psychiatric impairment did not deteriorate in most people who were taking chenodeoxycholic acid. The results of the studies should be interpreted with caution because they are small (n=35 and n=28), uncontrolled, retrospective studies. Data were commonly missing across the time points and many people received additional treatments as well as chenodeoxycholic acid, which may disguise the true treatment effect of chenodeoxycholic acid. Outcomes were reported as improved, stabilised or deteriorated but these are not defined. The weaknesses in the studies' design and conduct mean they are subject to bias and confounding, are difficult to interpret and
	CDCA-STRCH-CR-14-001	5/10	Directly applicable		

					cannot support firm conclusions. Also, there is little information available about what the broad term 'psychiatric impairment' includes.
Neurological impairment	CDCA-STUK-15-001	5/10	Directly applicable	B	This outcome compared the number of people with neurological impairment before and after chenodeoxycholic acid to see if treatment reduced this symptom. In CDCA-STUK-15-001, 20/31 people (65%) had neurological impairment at baseline, which reduced to 17/31 people (55%) at the most recent clinical visit. Polyneuropathy, pyramidal dysfunction and cerebellar dysfunction (types of neurological impairment) stabilised or improved in 11/11 people (100%), 9/15 people (60%) and 12/14 people (86%) respectively. By contrast, about half of people with neurological impairment in CDCA-STRCH-CR-14-001 got worse in spite of treatment. 26/97 people (29%) got worse in the literature review in the European public assessment report. Neuropathy was assessed by measuring how well the nerves conduct signals in the study by del Mar Amador et al. and, overall, significant improvements were seen with chenodeoxycholic acid. In summary, in CDCA-STUK-15-001 with the younger population (mean age 26 years), who were at an earlier stage of the disease, chenodeoxycholic acid may have helped to reduce or cease the deterioration of neurological impairment in most people. However, in CDCA-STRCH-CR-14-001 with the older population (mean age 35 years) with worse disability scores at baseline, chenodeoxycholic acid did not appear to have an effect on the deterioration of neurological impairment in many people. The results of the studies should be interpreted with caution because they are small (n=35 and n=28), uncontrolled, retrospective studies. Data were commonly missing across the time points and many people received additional treatments as well as chenodeoxycholic acid, which may disguise the true treatment effect of chenodeoxycholic acid. Outcomes were reported as improved, stabilised or deteriorated but these are not defined. 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.
	CDCA-STRCH-CR-14-001	5/10	Directly applicable		
Neurological disability measured using the Rankin Scale score	CDCA-STUK-15-001	5/10	Directly applicable	B	The Rankin scale is a tool that is used to rate a person's level of disability and dependence. Scores range from 0 (perfect health without symptoms) to 6 (death). This outcome looked at how the score changed from baseline with chenodeoxycholic acid treatment. In CDCA-STUK-15-001, Rankin scale scores improved in 4/26 people (15%), stabilised in 18/26 people (69%) and deteriorated in 4/26 people (15%). Overall, mean Rankin scale scores deteriorated by a small amount between baseline and the most recent clinical visit. However, these changes were not statistically
	CDCA-STRCH-CR-14-001	5/10	Directly applicable		

					significant. Results of CDCA-STRCH-CR-14-001 were generally similar although Rankin scores worsened in a higher proportion of people than in CDCA-STUK-15-001, and the overall deterioration in scores was statistically significant at 2 out of 3 time points. Note that people in CDCA-STRCH-CR-14-001 were, on average, older and had higher disability scores at baseline. In summary, the results suggest that chenodeoxycholic acid may reduce the deterioration in Rankin scale scores, with the chances of success increasing in younger people, who were at an earlier stage of the disease. The results of the studies should be interpreted with caution because they are small (n=35 and n=28), uncontrolled, retrospective studies. Data were commonly missing across the time points and many people received additional treatments as well as chenodeoxycholic acid, which may disguise the true treatment effect of chenodeoxycholic acid. Outcomes were reported as improved, stabilised or deteriorated but these are not defined. 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.
Neurological disability measured using the Expanded Disability Status Scale (EDSS)	CDCA-STUK-15-001	5/10	Directly applicable	B	The EDSS is another tool that is used to rate a person's level of disability. The scores range from 0 to 10, with 0.5 unit increments representing higher levels of disability. 10 indicates death. This outcome looked at how the score changed from baseline with chenodeoxycholic acid treatment. In CDCA-STUK-15-001, EDSS scores improved in 6/26 people (23%), stabilised in 14/26 people (54%) and deteriorated in 6/26 people (23%). Overall, mean EDSS scores deteriorated by a small amount between baseline and the most recent clinical visit. However, these changes were not statistically significant. Results of CDCA-STRCH-CR-14-001 were generally similar although EDSS scores worsened in a higher proportion of people than in CDCA-STUK-15-001, and the overall deterioration in scores was statistically significant at all time points. Note that people in CDCA-STRCH-CR-14-001 were, on average, older and had higher disability scores at baseline. Similar results were seen in the study by del Mar Amador et al. In summary, the results suggest that chenodeoxycholic acid may reduce the deterioration in EDSS scores, with the chances of success increasing in younger people, who were at an earlier stage of the disease. The results of the studies should be interpreted with caution because they are small (n=35, n=28 and n=14), uncontrolled, retrospective studies. In the 2 main studies, data were commonly missing across the time points and many people received additional treatments as well as chenodeoxycholic acid, which may disguise the true treatment effect of chenodeoxycholic acid. Outcomes were reported as improved,
	CDCA-STRCH-CR-14-001	5/10	Directly applicable		
	Del Mar Amador et al. (2018)	4/10	Directly applicable		
	CDCA-STRCH-CR-14-001	5/10	Directly applicable		

					stabilised or deteriorated but these are not defined. 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.
Treatment-emergent and treatment-related adverse events	CDCA-STUK-15-001	5/10	Directly applicable	B	Treatment-emergent adverse events are undesirable events that were not present before the treatment started, or events that were already present but which worsened in intensity or frequency after the treatment. The adverse event may or may not be associated with the treatment. Treatment-related adverse events are adverse events that are considered to be related to the treatment being investigated in the study. This outcome looks at how many treatment-emergent and treatment-related adverse events occurred during the study. In CDCA-STUK-15-001, 76 treatment-emergent adverse events were reported in 26/35 people (74.3%). 9/76 treatment-emergent adverse events in 7 people were considered to be serious. There were 16 treatment-emergent adverse events in 9/28 people (32.1%) in CDCA-STRCH-CR-14-001, which were all considered to be serious. In CDCA-STUK-15-001, 3 adverse events were considered to be related to chenodeoxycholic acid treatment. These were constipation in 2 people and toxic hepatitis in 1 person, which were not thought to be serious. No adverse events were considered to be treatment-related in CDCA-STRCH-CR-14-001. Treatment was reported to be 'well tolerated' in people in the study by del Mar Amador et al. In summary, adverse events reported with chenodeoxycholic acid in the studies were generally not serious and were considered to be mostly related to the underlying disease condition, rather than the treatment itself. The results of the studies should be interpreted with caution because they are small (n=35, n=28 and n=14, uncontrolled, retrospective studies. In the 2 main studies, data were commonly missing across the time points and many people received additional treatments as well as chenodeoxycholic 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.
	CDCA-STRCH-CR-14-001	5/10	Directly applicable		
	Del Mar Amador et al. (2018)	4/10	Directly applicable		

3 Related NICE guidance and NHS England clinical policies

NHS England and NICE have not issued any guidelines or policies on managing CTX with chenodeoxycholic acid.

4 References

Berginer VM, Salen G, and Shefer S (1984) Long-term treatment of cerebrotendinous xanthomatosis with chenodeoxycholic acid. The New England Journal of Medicine 311(26): 1649-52

del Mar Amador M, Masingue M, Debs R et al. (2018) Treatment with chenodeoxycholic acid in cerebrotendinous xanthomatosis: clinical, neurophysiological, and quantitative brain structural outcomes. Journal of Inherited Metabolic Disease https://doi.org/10.1007/s10545-018-0162-7

Koopman BJ, Wolthers BG, van der Molen JC et al.(1988) Cerebrotendinous xanthomatosis: a review of biochemical findings of the patient population in The Netherlands. Journal of Inherited Metabolic Disease 11(1): 56-75

Waterreus RJ, Koopman B, Wolthers BG et al. (1987) Cerebrotendinous xanthomatosis (CTX): a clinical survey of the patient population in The Netherlands. Clinical Neurology and Neurosurgery 89(3): 169-75

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 + rerun 24th January 2018
Number of results retrieved: 160 + 19 on rerun
Search strategy:

1 exp Chenodeoxycholic Acid/ (3631)
2 chenodeoxychol*.tw. (3397)
3 chenodesoxychol*.tw. (70)
4 chemodeoxychol*.tw. (9)
5 (cholan* adj3 acid).tw. (472)
6 anthropodeoxychol*.tw. (0)
7 anthropodesoxychol*.tw. (0)
8 aylehning.tw. (0)
9 chebil.tw. (1)
10 chenar.tw. (1)
11 chendol.tw. (0)
12 chenic acid.tw. (37)
13 chenix.tw. (2)
14 cheno.tw. (64)
15 chenocedon.tw. (0)
16 chenocedon.tw. (0)
17 chenocol.tw. (0)
18 chenodex.tw. (0)
19 chenodiol.tw. (39)
20 chenodol.tw. (0)
21 chenofalk.tw. (1)
22 chenossil.tw. (0)
23 xenbilox.tw. (0)
24 cholanol.tw. (2)
25 cholasa.tw. (0)
26 fluibil.tw. (0)
27 gallodeoxycholic.tw. (0)
28 gallodesoxycholic.tw. (0)
29 hekbilin.tw. (0)
30 kebilis.tw. (1)
31 quenobilan.tw. (0)
32 quenocol.tw. (0)
33 regalen.tw. (0)
34 soluston.tw. (0)
35 theramatic.tw. (0)
36 hydroxylithocholic.tw. (3)
37 anthropodeoxycholic.tw. (0)
38 anthropodesoxycholic.tw. (0)
39 chenique.tw. (0)
40 chenophalk.tw. (1)
41 henohol.tw. (1)
42 cdca.tw. (832)

43 or/1-42 (5772)
44 Xanthomatosis, Cerebrotendinous/ (292)
45 cerebrotendinous xanthomatosis.tw. (605)
46 cholestanolosis.tw. (6)
47 ctx.tw. (9622)
48 (xanthamatosis or xanthamatoses).tw. (0)
49 (cholesterinosis or cholesterinoses).tw. (16)
50 van bogaert scherer epstein.tw. (4)
51 or/44-50 (10011)
52 43 and 51 (195)
53 animals/ not (humans/ and animals/) (4498046)
54 52 not 53 (192)
55 54 (192)
56 limit 55 to english language (160)
57 CDCA-STUK-15-001.af. (0)
58 CDCA-STRCH-CR-14-001.af. (0)
59 or/56-58 (160)

Database: Embase

Platform: Ovid
Version: 1974 to day before search date
Search date: 1st September 2017 + rerun 24th January 2018
Number of results retrieved: 273 + 9 on rerun
Search strategy:

1 chenodeoxycholic acid/ (5244)
2 chenodeoxychol*.tw. (4157)
3 chenodesoxychol*.tw. (105)
4 chemodeoxychol*.tw. (18)
5 (cholan* adj3 acid).tw. (503)
6 anthropodeoxychol*.tw. (0)
7 anthropodesoxychol*.tw. (0)
8 aylehning.tw. (0)
9 chebil.tw. (0)
10 chenar.tw. (9)
11 chendol.tw. (27)
12 chenic acid.tw. (46)
13 chenix.tw. (29)
14 cheno.tw. (79)
15 chenocedon.tw. (1)
16 chenocedon.tw. (1)
17 chenocol.tw. (1)
18 chenodex.tw. (16)
19 chenodiol.tw. (60)
20 chenodol.tw. (0)
21 chenofalk.tw. (75)
22 chenossil.tw. (8)
23 xenbilox.tw. (2)
24 cholanol.tw. (2)
25 cholasa.tw. (0)
26 fluibil.tw. (5)
27 gallodeoxycholic.tw. (0)
28 gallodesoxycholic.tw. (0)

29 hekbilin.tw. (11)
30 kebilis.tw. (6)
31 quenobilan.tw. (1)
32 quenocol.tw. (0)
33 regalen.tw. (3)
34 soluston.tw. (0)
35 theramatic.tw. (0)
36 hydroxylithocholic.tw. (3)
37 anthropodeoxycholic.tw. (0)
38 anthropodesoxycholic.tw. (0)
39 chenique.tw. (0)
40 chenophalk.tw. (1)
41 henohol.tw. (1)
42 cdca.tw. (1214)
43 or/1-42 (7028)
44 cerebrotendinous xanthomatosis/ (797)
45 cerebrotendinous xanthomatosis.tw. (722)
46 cholestanolosis.tw. (7)
47 ctx.tw. (14300)
48 (xanthamatosis or xanthamatoses).tw. (1)
49 (cholesterinosis or cholesterinoses).tw. (13)
50 van bogaert scherer epstein.tw. (7)
51 or/44-50 (14867)
52 43 and 51 (322)
53 nonhuman/ not (human/ and nonhuman/) (4052839)
54 52 not 53 (319)
55 54 (319)
56 limit 55 to english language (273)
57 CDCA-STUK-15-001.af. (0)
58 CDCA-STRCH-CR-14-001.af. (0)
59 or/56-58 (273)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:

CDSR – 8 of 12, 2017 (original searches); 1 of 12, 2018 (rerun searches)
DARE – 2 of 4, April 2015 (legacy database)
CENTRAL – 7 of 12, July 2017; 12 of 12, 2017 (rerun searches)
HTA – 4 of 4, October 2016
NHS EED – 2 of 4, April 2015 (legacy database)

Search date: 1st September 2017
Number of results retrieved: CDSR – 0; DARE – 0; CENTRAL – 1; HTA – 0; NHS EED – 0.
No additional results on rerun.
Search strategy:

ID Search
#1 [mh "Chenodeoxycholic Acid"]
#2 chenodeoxychol*:ti,ab
#3 chenodesoxychol*:ti,ab
#4 chemodeoxychol*:ti,ab
#5 (cholan* near/3 acid):ti,ab
#6 anthropodeoxychol*:ti,ab
#7 anthropodesoxychol*:ti,ab

#8 aylehning:ti,ab
#9 chebil:ti,ab
#10 chenar:ti,ab
#11 chendol:ti,ab
#12 chenic acid:ti,ab
#13 chenix:ti,ab
#14 cheno:ti,ab
#15 chenocedon:ti,ab
#16 chenocol:ti,ab
#17 chenodex:ti,ab
#18 chenodiol:ti,ab
#19 chenodol:ti,ab
#20 chenofalk:ti,ab
#21 chenossil:ti,ab
#22 cholanol:ti,ab
#23 cholasa:ti,ab
#24 fluibil:ti,ab
#25 gallodeoxycholic:ti,ab
#26 gallodesoxycholic:ti,ab
#27 hekbilin:ti,ab
#28 kebilis:ti,ab
#29 quenobilan:ti,ab
#30 quenocol:ti,ab
#31 regalen:ti,ab
#32 soluston:ti,ab
#33 theramatic:ti,ab
#34 hydroxylithocholic:ti,ab
#35 anthropodeoxycholic:ti,ab
#36 anthropodesoxycholic:ti,ab
#37 chenique:ti,ab
#38 chenophalk:ti,ab
#39 henohol:ti,ab
#40 cdca:ti,ab
#41 xenbilox:ti,ab
#42 {or #1-#41}
#43 [mh ^"Xanthomatosis, Cerebrotendinous"]
#44 cerebrotendinous xanthomatosis:ti,ab
#45 cholestanolosis:ti,ab
#46 ctx:ti,ab
#47 (xanthamatosis or xanthamatoses):ti,ab
#48 (cholesterinosis or cholesterinoses):ti,ab
#49 van bogaert scherer epstein:ti,ab
#50 {or #43-#49}
#51 #42 and #50
#52 "CDCA-STUK-15-001"
#53 "CDCA-STRCH-CR-14-001"
#54 #51 or #52 or #53

Appendix 2 Study selection

The search strategy presented in appendix 1 yielded 292 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 sterol 27-hydroxylase deficiency (presenting as CTX).	Non-humans People with other bile acid synthesis disorders
Intervention	Chenodeoxycholic acid, alone or in combination with other treatments (such as statins)	
Comparator	• Standard care without chenodeoxycholic acid or cholic acid • Other bile acids (such as cholic acid and ursodeoxycholic acid) • Statins • Combination regimens involving cholic acid and chenodeoxycholic acid • Nutraceuticals • Placebo	
Outcomes	• Mortality • Liver disease (including need for liver transplantation and change in liver histology) • Neurological disease (including cognitive dysfunction and epilepsy) • Height and weight change • Complications such as rickets, bleeding diathesis, night blindness, and neuroaxonal dystrophy • Cataract, diarrhea, ataxia with xanthoma • Laboratory test results (for example, bile acids, liver transaminases and bilirubin) • Need for vitamin supplementation • Avoidance of atherosclerosis • Regression of xanthomata • Disability measures • Health-related quality of life • Adverse effects	

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 Studies looking at diagnosis, complications, presentations and genetic mutations, rather than treatment outcomes

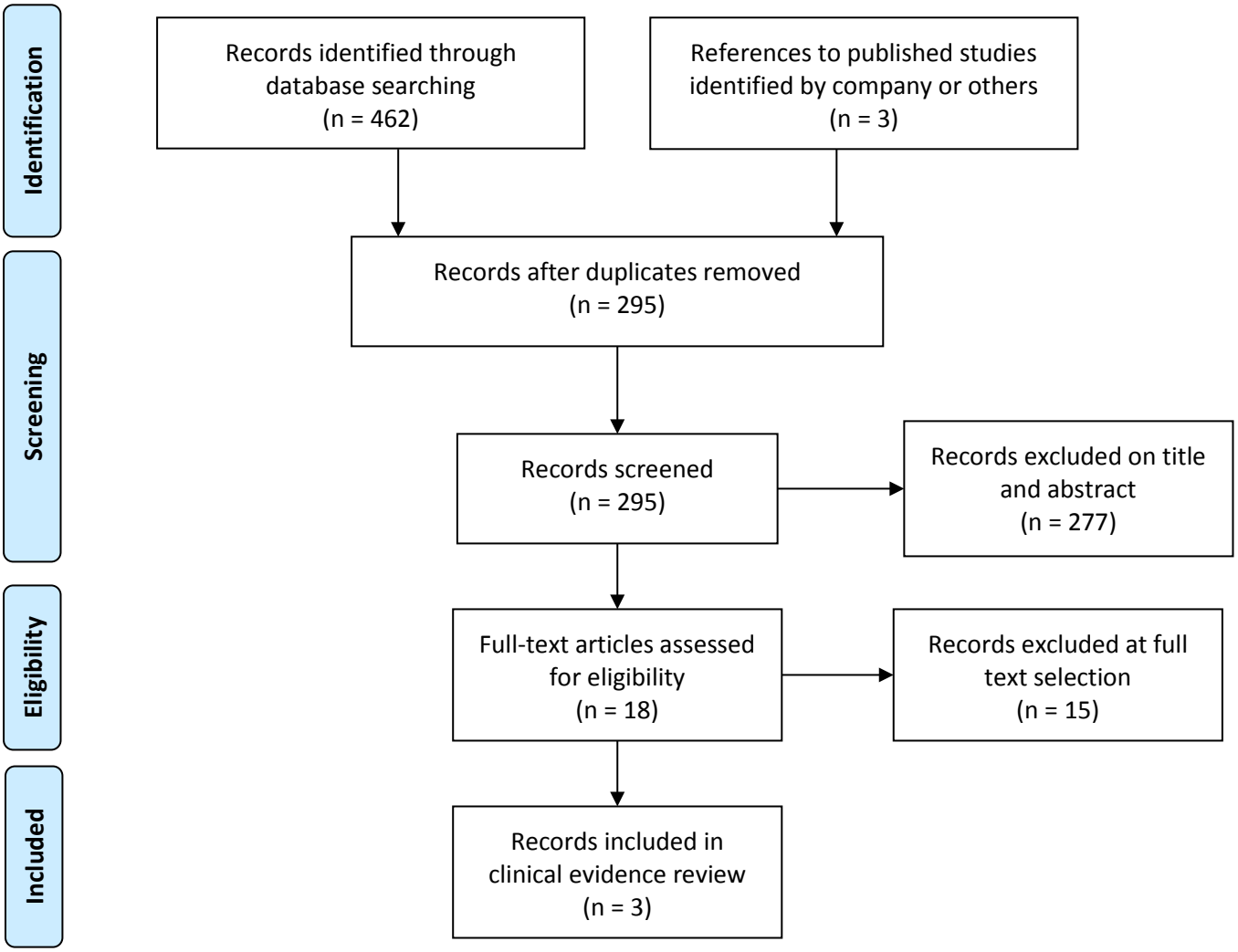
Fifteen full text references were obtained and assessed for relevance. Of these, none are included in the evidence summary. All 15 references were excluded and are listed in table 3.

Table 3 Studies excluded at full text

Study reference	Reason for exclusion
Berginer VM, Salen G and Shefer S (1984) Long-term treatment of cerebrotendinous xanthomatosis with chenodeoxycholic acid. The New England Journal of Medicine 311(26): 1649–52	Included in literature review in EPAR
Ginanneschi F, Mignarri A, Mondelli M et al. (2013) Polyneuropathy in cerebrotendinous xanthomatosis and response to treatment with chenodeoxycholic acid. Journal of Neurology 260(1): 268–74	Included in literature review in EPAR
Koopman BJ (1988) Cerebrotendinous xanthomatosis and other inborn errors of metabolism in bile acid synthesis. Pharmaceutisch Weekblad - Scientific Edition 10(3): 130–2	Non-English language
Koopman BJ, Wolthers BG, van der Molen JC et al (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	Case series with less than 14 people
Koopman BJ, Wolthers BG, van der Molen JC et al. (1988) Cerebrotendinous xanthomatosis: a review of biochemical findings of the patient population in The Netherlands. Journal of Inherited Metabolic Disease 11(1): 56–75	Included in literature review in EPAR
Mignarri A, Magni A, Del Puppo M et al. (2016) Evaluation of cholesterol metabolism in	Data significantly overlaps with data in

cerebrotendinous xanthomatosis. Journal of Inherited Metabolic Disease 39(1): 75–83	CDCA-STRCH-CR-14-001 in the EPAR
Mignarri A, Dotti MT, Federico A et al. (2017) The spectrum of magnetic resonance findings in cerebrotendinous xanthomatosis: redefinition and evidence of new markers of disease progression. Journal of Neurology 264(5): 862–74	Data significantly overlaps with data in CDCA-STRCH-CR-14-001 in the EPAR
Nadjar Y, Couvert P, Lamari F et al. (2015) Natural history of cerebrotendinous xanthomatosis: a pediatric disease diagnosed in adults. European Journal of Neurology 22: 358	Abstract only
Pilo B, Sobrido MJ, Martin-Moro JG et al (2009) Cerebrotendinous xanthomatosis in Spain. European Journal of Neurology 16(S3): 295	Abstract only
Pilo-de-la-Fuente B, Jimenez-Escrig A, Lorenzo JR et al. (2011) Cerebrotendinous xanthomatosis in Spain: clinical, prognostic, and genetic survey. European Journal of Neurology 18(10): 1203–11	Included in literature review in EPAR
Schaefer E, Salen G, Polisecki E et al. (2017) The diagnosis and treatment of cerebrotendinous xanthomatosis. Journal of Clinical Lipidology 11(3): 774–5	Abstract only
Sekijima Y, Koyama S, Inaba Y et al. (2017) Nationwide survey on cerebrotendinous xanthomatosis in Japan. Journal of the Neurological Sciences 381(Supplement 1): 703	Abstract only
Waterreus RJ, Koopman BJ, Wolthers BG et al. (1987) Cerebrotendinous xanthomatosis (CTX): a clinical survey of the patient population in The Netherlands. Clinical neurology and neurosurgery 89(3): 169–75	Included in literature review in EPAR
Wolthers BG, Volmer M, van der Molen J et al. (1983) Diagnosis of cerebrotendinous xanthomatosis (CTX) and effect of chenodeoxycholic acid therapy by analysis of urine using capillary gas chromatography. Clinica Chimica Acta, and International Journal of Clinical Chemistry 131(1-2): 53–65	Case series with less than 14 people
Yahalom G, Tsabari R, Molshatzki N et al. (2013) Neurological outcome in cerebrotendinous xanthomatosis treated with chenodeoxycholic acid: early versus late diagnosis. Clinical neuropharmacology 36(3): 78–83	Included in literature review in EPAR
Abbreviations: EPAR, European public assessment report	

Figure 1 Flow chart of included studies



Appendix 3 Evidence tables

Table 4 CDCA-STUK-15-001

Study reference	**Retrospective cohort study to investigate the safety and efficacy of chenodeoxycholic acid in patients affected by cerebrotendinous xanthomatosis**
Unique identifier	CDCA-STUK-15-001
Study type (and NSF-LTC study code)	Retrospective cohort study using data from medical charts P1: Primary research using quantitative approaches
Aim of the study	To evaluate: • the effects of chenodeoxycholic acid on serum cholestanol levels and, in selected cases, urinary bile alcohols • the effects of chenodeoxycholic acid on disease progression (by measuring disability scores, electrophysiological data, imaging data, laboratory parameters and/or disease signs and symptoms) • The safety and tolerability of chenodeoxycholic acid
Study dates	The last data point in the trial was 3 June 2015
Setting	1 centre in the Netherlands
Number of participants	35 people. (All completed the study; however, data were missing in more than 25% of participants for some outcomes)
Population	People who had had CTX for at least 1 year who had received treatment with chenodeoxycholic acid
Inclusion criteria	• Age between 2 and 75 years. (At the first treatment, 15 people were aged <21 years and 20 were aged ≥21 years) • At least 1 cholestanol level and/or urinary bile alcohol level no more than 3 months prior to treatment with chenodeoxycholic acid • At least 1 cholestanol level and/or urinary bile alcohol level post-treatment within 2 years of starting chenodeoxycholic acid • If not available, qualitative assessment of cholestanol and/or urinary bile alcohols as recorded in the notes could be considered
Exclusion criteria	No pre-determined exclusion criteria were defined in the study protocol
Intervention(s)	Oral chenodeoxycholic acid 750 mg/day or 15 mg/kg/day. (The median dose at the screening visit was 750 mg [range 225–1000 mg])
Comparator(s)	None
Length of follow-up	Data were collected from the beginning of treatment up to 2 years after (with a minimum of 1 year) and at the most recent clinical visit. (The mean duration of treatment was 10.74 years ±6.66 years)
Outcomes	On-treatment assessments were compared to assessments at baseline[1] and outcomes included: • Serum levels of cholestanol • Urinary bile alcohol measurements • Disease signs and symptoms

	• Neurological disability scale scores (Rankin scale score[2] or EDSS score[3]) • Cognitive impairment • Adverse events
Source of funding	Not known

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 questions are listed and the design is described
2. Is the research design appropriate for the aims and objectives of the research?	1/2	The study was a retrospective cohort 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 Although it is difficult to perform high-quality studies in rare diseases with limited treatment options (such as CTX), it may have been preferable to perform a prospective study of the effects of treatment with chenodeoxycholic acid. The EPAR notes that long-term, multicentre controlled clinical studies would not be feasible in this population
3. Are the methods clearly described?	1/2	The methods are described. However, the EPAR highlights weaknesses in the design and conduct of the study; for example, missing data
4. Are the data adequate to support the authors' interpretations / conclusions?	0/2	As noted in the EPAR, the data are difficult to interpret and are not adequate to support firm conclusions. 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 study was undertaken in the Netherlands, where treatment pathways may differ from the UK population. Also there is considerable variation in the characteristics of individual people with CTX
Total	5/10	
Applicability	Directly / indirectly applicable	Directly applicable: a direct study that focusses on people with the indication and characteristics of interest

[1] Post treatment assessments were from 3 visits: post treatment visit 1, post treatment visit 2 and clinical current visit. The visits were at different intervals for each of the participants. To include as complete a data set as possible, the data collection for post treatment visit 1 and 2 was not restricted to the 2 years post treatment specified in the protocol

[2] The Rankin scale is a tool used to measure the level of a person's disability and dependence and ranges from 0 (perfect health without symptoms) to 6 (death)

[3] The EDSS is a tool used to rate a person's level of disability. It ranges from 0 to 10, with 0.5 unit increments representing higher levels of disability. 10 indicates death

Abbreviations: CTX, Cerebrotendinous xanthomatosis; EDSS, Expanded Disability Status Scale; EPAR, European public assessment report

Table 5 CDCA-STRCH-CR-14-001

Study reference	**Retrospective cohort study to investigate the safety and efficacy of chenodeoxycholic acid in patients affected by cerebrotendinous xanthomatosis**
Unique identifier	CDCA-STRCH-CR-14-001
Study type (and NSF-LTC study code)	Retrospective cohort study using data from medical charts P1: Primary research using quantitative approaches
Aim of the study	To evaluate: • the effects of chenodeoxycholic acid on serum cholestanol levels and, in selected cases, other bile acid precursors • the effects of chenodeoxycholic acid on disease progression (by measuring disability scores, electrophysiological data, imaging data, laboratory parameters and bone mineral density) • The safety and tolerability of chenodeoxycholic acid
Study dates	The last data point in the trial was 22 October 2014
Setting	1 centre in Italy
Number of participants	28 people. (25 completed the study)
Population	People who had had CTX for at least 1 year who had received treatment with chenodeoxycholic acid

Inclusion criteria	• Age between 2 and 75 years • At least 1 cholestanol level and 1 routine laboratory evaluation no more than 3 months prior to treatment with chenodeoxycholic acid • At least 1 cholestanol level and 1 routine laboratory evaluation post-treatment within 2 years of starting chenodeoxycholic acid
Exclusion criteria	The EPAR does not report whether any pre-determined exclusion criteria were defined in the study protocol or not
Intervention(s)	Oral chenodeoxycholic acid 750 mg/day. (The median dose at the screening visit was 750 mg [range 500–750mg])
Comparator(s)	None
Length of follow-up	Data were collected from the beginning of treatment up to 2 years after (with a minimum of 1 year) and at the most recent clinical visit. (The median follow-up was 5.75 years [range 0–25 years])
Outcomes	On-treatment assessments were compared to assessments at baseline[1] and outcomes included: • Serum levels of cholestanol • Neurological disability scale scores (Rankin scale score[2] or EDSS score[3]) • Cognitive impairment • Bone mineral density • Adverse events
Source of funding	Not known

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 questions are listed and the design is described
2. Is the research design appropriate for the aims and objectives of the research?	1/2	The study was a retrospective cohort 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 Although it is difficult to perform high-quality studies in rare diseases with limited treatment options (such

		as CTX), it may have been preferable to perform a prospective study of the effects of treatment with chenodeoxycholic acid. The EPAR notes that long-term, multicentre controlled clinical studies would not be feasible in this population
3. Are the methods clearly described?	1/2	The methods are described. However, the EPAR highlights weaknesses in the design and conduct of the study; for example, missing data
4. Are the data adequate to support the authors' interpretations / conclusions?	0/2	As noted in the EPAR, the data are difficult to interpret and are not adequate to support firm conclusions. 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 study was undertaken in Italy, where treatment pathways may differ from the UK population. Also there is considerable variation in the characteristics of individual people with CTX
Total	5/10	
Applicability	Directly / indirectly applicable	Directly applicable: a direct study that focusses on people with the indication and characteristics of interest
[1] Post treatment assessments were from 3 visits: post treatment visit 1, post treatment visit 2 and clinical current visit [2] The Rankin scale is a tool used to measure the level of a person's disability and dependence and ranges from 0 (perfect health without symptoms) to 6 (death) [3] The EDSS is a tool used to rate a person's level of disability. It ranges from 0 to 10, with 0.5 unit increments representing higher levels of disability. 10 indicates death		
Abbreviations: CTX, Cerebrotendinous xanthomatosis; EDSS, Expanded Disability Status Scale; EPAR, European public assessment report		

Table 6 del Mar Armador et al. 2018

Study reference	del Mar Amador M, Masingue M, Debs R et al. (2018) Treatment with chenodeoxycholic acid in cerebrotendinous xanthomatosis: clinical,

	neurophysiological, and quantitative brain structural outcomes. Journal of Inherited Metabolic Disease https://doi.org/10.1007/s10545-018-0162-7
Unique identifier	None
Study type (and NSF-LTC study code)	Retrospective observational study P1: Primary research using quantitative approaches
Aim of the study	Not clearly stated. Evaluated the effect of chenodeoxycholic acid on brain structural, clinical and neurophysiological parameters in people with CTX
Study dates	Data were retrospectively collected between 2007 and 2017
Setting	1 centre in France
Number of participants	14 people
Population	People with CTX who had received treatment with chenodeoxycholic acid There were 3 males and 11 females belonging to 10 families, with a mean age at evaluation of 29±15 years (range 8 to 59 years)
Inclusion criteria	No predetermined inclusion criteria were reported in the paper
Exclusion criteria	No predetermined exclusion criteria were reported in the paper
Intervention(s)	Chenodeoxycholic acid Dosage does not appear to have been prespecified, and the dosages used by people in the study have not been reported in the paper
Comparator(s)	None
Length of follow-up	Mean follow-up was 5 years (range 2 to 9 years)
Outcomes	Not clearly stated. On-treatment assessments were compared to assessments at baseline and outcomes included: • Serum levels of cholestanol • Disease severity (measured by EDSS score[1]) • Ataxia severity (measured by SARA score[2]) • Neuropathy (assessed using electroneuromyography, which measures nerve conduction) • Brain structure (measured by MRI, using volumetric analysis and diffusion weighted imaging)
Source of funding	This study was supported the Investissements d'Avenir (Paris Institute of Neurosciences – IHU)

NSF-LTC		
Criteria	**Score**	**Narrative description of study quality**

1. Are the research questions/aims and design clearly stated?	0/2	The study did not clearly define the research question. Although the design was briefly stated, there were no clear details of the methods used
2. Is the research design appropriate for the aims and objectives of the research?	1/2	The study was a retrospective cohort 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 Although it is difficult to perform high-quality studies in rare diseases with limited treatment options (such as CTX), it may have been preferable to perform a prospective study of the effects of treatment with chenodeoxycholic acid
3. Are the methods clearly described?	1/2	The methods are partially described. Although the methods for assessing the outcomes have been described, there is no detail about how retrospective data were collected.
4. Are the data adequate to support the authors' interpretations / conclusions?	1/2	The study is retrospective, included only 14 people and does not have a control group. Therefore, the data is subject to bias and confounding and cannot support firm conclusions. Some of the conclusions in the paper are based on small subgroups of people in the study
5. Are the results generalisable?	1/2	The study was undertaken in France where treatment pathways may differ from the UK population. Also there is considerable variation in the characteristics of individual people with CTX
Total	4/10	
Applicability	Directly / indirectly applicable	Directly applicable: a direct study that focusses on people with the indication and characteristics of interest

[1] The EDSS is a tool used to rate a person's level of disability. It ranges from 0 to 10, with 0.5 unit increments representing higher levels of disability. 10 indicates death

[2] The SARA is a tool used to assess and rate a person's level of ataxia. It ranges from 0 (no cerebellar symptoms) to 40 (most severe cerebellar symptoms). SARA was assessed in 6 people only

Abbreviations: CTX, Cerebrotendinous xanthomatosis; EDSS, Expanded Disability Status Scale; MRI, Magnetic resonance imaging; SARA, Scale for the assessment and rating of ataxia

Appendix 4 Results tables

Table 7 CDCA-STUK-15-001

Changes from baseline with chenodeoxycholic acid treatment		
Mean serum levels (micromol/litre) of cholestanol (SD)	Post treatment visit 1 (n=23)	19.4 (±14.3) compared with 75.8 (±39.3) at baseline Difference −56.4 (95% CI −73.5 to −39.3) Statistically significant improvement, p<0.001
	Post treatment visit 2 (n=25)	7.7 (±3.6) compared with 76.3 (±40.0) at baseline Difference −68.6 (95% CI −85.0 to −52.3) Statistically significant improvement, p<0.001
	Most recent clinical visit (n=23)	9.1 (±6.5) compared with 72.1 (±38.4) at baseline Difference −63.0 (95% CI −80.1 to −45.9) Statistically significant improvement, p<0.001
Urinary bile alcohol measurements	Baseline	All patients had raised urinary bile alcohols
	Post treatment visit 1	18/21 patients improved (85.7%) Statistically significant, p<0.001
	Post treatment visit 2	19/19 patients improved (100%) Statistically significant, p<0.001
	Most recent clinical visit	11/14 patients improved (78.6%) Statistically significant, p<0.001
Diarrhoea	Baseline	23/31 patients (74.2%) had diarrhoea
	Post treatment visit 1	2/29 patients (6.9%) had diarrhoea
	Post treatment visit 2	3/30 patients (10.0%) had diarrhoea
	Most recent clinical visit	0/31 patients (0%) had diarrhoea Diarrhoea resolved in all 23 patients (100%) who had diarrhoea at baseline No statistical analyses were reported for this outcome
Xanthomas	Baseline	8/31 patients (25.8%) had xanthomas
	Post treatment visit 1	8/29 patients (27.6%) had xanthomas
	Post treatment visit 2	8/30 patients (26.7%) had xanthomas
	Most recent clinical visit	10/31 patients (32.3%) had xanthomas It is not reported whether xanthomas improved, stabilised or deteriorated No statistical analyses were reported for this outcome
Cataracts	Baseline	10/31 (32.3%) patients had cataracts
	Post treatment visit 1	6/29 patients (20.7%) had cataracts
	Post treatment visit 2	4/30 patients (13.3%) had cataracts

	Most recent clinical visit	0/31 patients (0%) had cataracts Improvement was mostly driven by the removal of cataracts in 20/31 patients (64.5%) No statistical analyses were reported for this outcome
Cognitive impairment	Baseline	18/31 patients (58.1%) had cognitive impairment
	Post treatment visit 1	17/29 patients (58.6%) had cognitive impairment
	Post treatment visit 2	18/30 patients (60.0%) had cognitive impairment
	Most recent clinical visit	16/31 patients (51.6%) had cognitive impairment In these 16 patients, cognitive impairment improved in 1 and stabilised in 15 Cognitive impairment improved or stabilised in all 18 patients (100%) with cognitive impairment at baseline No statistical analyses were reported for this outcome
Psychiatric impairment	Baseline	6/31 patients (19.4%) had psychiatric impairment
	Post treatment visit 1	4/29 patients (13.8%) had psychiatric impairment
	Post treatment visit 2	6/30 patients (20.0%) had psychiatric impairment
	Most recent clinical visit	5/31 patients (16.1%) had psychiatric impairment In these 5 patients, psychiatric impairment improved in 1 and stabilised in 4 Psychiatric impairment improved or stabilised in 6 patients (100%) with psychiatric impairment at baseline. Signs deteriorated in 1 person who did not have symptoms at baseline No statistical analyses were reported for this outcome
Neurological impairment	Baseline	20/31 patients (64.5%) had neurological impairment
	Post treatment visit 1	17/29 patients (58.6%) had neurological impairment
	Post treatment visit 2	19/30 patients (63.3%) had neurological impairment
	Most recent clinical visit	17/31 patients (54.8%) had neurological impairment Pyramidal signs of neurological impairment improved or stabilised in 9/15 patients (60%) who experienced them at baseline, and deteriorated in 6/15 patients (40%). Pyramidal

		signs deteriorated in 6 people who did not have them at baseline Cerebellar signs of neurological impairment improved or stabilised in 12/14 patients (85.7%) who experienced them at baseline, and deteriorated in 2/4 patients (14.3%). Cerebellar signs deteriorated in 2 people who did not have them at baseline Polyneuropathy improved or stabilised in 11/11 patients (100%) who experienced this at baseline Parkinsonism deteriorated in 2 people who did not have it at baseline No statistical analyses were reported for this outcome
Mean Rankin scale score[1] (SD)	Post treatment visit 1 (n=25)	1.32 (±1.28) compared with 1.20 (±1.28) at baseline Difference 0.12 (95% CI −0.02 to 0.26) Non-significant deterioration
	Post treatment visit 2 (n=22)	1.55 (±1.34) compared with 1.32 (±1.32) at baseline Difference 0.23 (95% CI −0.01 to 0.46) Non-significant deterioration
	Most recent clinical visit (n=26)	1.12 (±1.34) compared with 1.04 (±1.15) at baseline Difference 0.08 (95% CI −0.22 to 0.38) Non-significant deterioration Rankin scale scores improved in 4/26 patients (15.4%), stabilised in 18/26 patients (69.2%) and deteriorated in 4/26 patients (15.4%)
Mean EDSS score[2] (SD)	Post treatment visit 1 (n=25)	2.10 (±2.21) compared with 1.98 (±2.19) at baseline Difference 0.12 (95% CI −0.08 to 0.32) Non-significant deterioration
	Post treatment visit 2 (n=22)	2.43 (±2.48) compared with 2.18 (±2.24) at baseline Difference 0.25 (95% CI −0.12 to 0.62) Non-significant deterioration
	Most recent clinical visit (n=26)	1.88 (±2.59) compared with 1.62 (±1.88) at baseline Difference 0.27 (95% CI −0.23 to 0.77) Non-significant deterioration EDSS scores improved in 6/26 patients (23.1%), stabilised in 14/26 patients (53.8%) and deteriorated in 6/26 patients (23.1%)
Adverse events	Treatment-emergent adverse events	76 events in 26/35 patients (74.3%)

	Serious treatment-emergent adverse events	9 events in 7/35 patients (20.0%)
	Treatment-related adverse events	3 non-serious events in 3/35 patients (8.6%) Constipation in 2 patients Toxic hepatitis in 1 patient
[1] The Rankin scale is a tool used to measure the level of a person's neurological disability and dependence and ranges from 0 (perfect health without symptoms) to 6 (death) [2] The EDSS is a tool used to rate a person's level of neurological disability. It ranges from 0 to 10, with 0.5 unit increments representing higher levels of disability. 10 indicates death		
Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; p, p value; SD, standard deviation		

Table 8 CDCA-STRCH-CR-14-001

Changes from baseline with chenodeoxycholic acid treatment		
Mean serum levels (mg/decilitre) of cholestanol (SD)	Post treatment visit 1 (n=23)	0.73 (±0.36) compared with 3.35 (±1.61) at baseline Difference −2.62 (95% CI −3.31 to −1.93) Statistically significant improvement, p<0.001
	Post treatment visit 2 (n=19)	0.54 (±0.24) compared with 3.38 (±1.09) at baseline Difference −2.84 (95% CI −3.32 to −2.37) Statistically significant improvement, p<0.001
	Most recent clinical visit (n=22)	0.94 (±1.28) compared with 3.63 (±1.49) at baseline Difference −2.68 (95% CI −3.46 to −1.90) Statistically significant improvement, p<0.001
Diarrhoea	Baseline	14/26 patients (53.8%) had diarrhoea
	Post treatment visit 1	11/26 patients (42.3%) had diarrhoea
	Post treatment visit 2	7/21 patients (33.3%) had diarrhoea
	Most recent clinical visit	11/26 patients (42.3%) had diarrhoea In these 11 patients, diarrhoea was stable in 9, improved in 1 and deteriorated in 1 No statistical analyses were reported for this outcome
Xanthomas	Baseline	21/26 patients (80.8%) had xanthomas
	Post treatment visit 1	21/26 patients (80.8%) had xanthomas
	Post treatment visit 2	18/21 patients (85.7%) had xanthomas
	Most recent clinical visit	21/26 patients (80.8%) had xanthomas In these 21 patients, xanthomas were stable in 15 and deteriorated in 6 No statistical analyses were reported for this outcome
Cataracts	Baseline	23/26 patients (88.5%) had cataracts

	Post treatment visit 1	23/26 patients (88.5%) had cataracts
	Post treatment visit 2	20/21 patients (95.2%) had cataracts
	Most recent clinical visit	23/26 patients (88.5%) had cataracts In these 23 patients, cataracts were stable in 22 and deteriorated in 1 No statistical analyses were reported for this outcome
Cognitive impairment	Baseline	20/26 patients (76.9%) had cognitive impairment
	Post treatment visit 1	21/26 patients (80.8%) had cognitive impairment
	Post treatment visit 2	16/21 patients (76.2%) had cognitive impairment
	Most recent clinical visit	22/26 patients (84.6%) had cognitive impairment In these 22 patients, cognitive impairment was stable in 16 and deteriorated in 6 No statistical analyses were reported for this outcome
Psychiatric impairment	Baseline	13/26 patients (50.0%) had psychiatric impairment
	Post treatment visit 1	13/26 patients (50.0%) had psychiatric impairment
	Post treatment visit 2	11/21 patients (52.4%) had psychiatric impairment
	Most recent clinical visit	13/26 patients (50.0%) had psychiatric impairment In these 13 patients, psychiatric impairment was stable in 12 and deteriorated in 1 No statistical analyses were reported for this outcome
Neurological impairment	Baseline	20/26 patients (76.9%) had neurological impairment
	Post treatment visit 1	20/26 patients (76.9%) had neurological impairment
	Post treatment visit 2	15/21 patients (71.4%) had neurological impairment
	Most recent clinical visit	20/26 patients (76.9%) had neurological impairment In these 20 patients, neurological impairment was stable in 9 and deteriorated in 11 No statistical analyses were reported for this outcome
Mean Rankin scale score[1] (SD)	Post treatment visit 1 (n=26)	2.3 (±1.3) compared with 2.0 (±1.2) at baseline Difference 0.3 (95% CI 0.1 to 0.5) Statistically significant deterioration, p=0.016
	Post treatment visit 2	2.0 (±1.2) compared with 1.8 (±1.2) at baseline

	(n=21)	Difference 0.1 (95% CI −0.0 to 03) Non-significant deterioration
	Most recent clinical visit (n=26)	2.5 (±1.4) compared with 2.0 (±1.2) at baseline Difference 0.5 (95% CI 0.2 to 0.7) Statistically significant deterioration, p=0.001 There was no deterioration in Rankin scale score in 16/26 patients (61.5%)
Mean EDSS score[2] (SD)	Post treatment visit 1 (n=26)	3.90 (±1.86) compared with 3.50 (±1.53) at baseline Difference 0.40 (95% CI 0.11 to 0.70) Statistically significant deterioration, p=0.010
	Post treatment visit 2 (n=21)	3.50 (±1.69) compared with 3.19 (±1.40) at baseline Difference 0.31 (95% CI 0.01 to 0.61) Statistically significant deterioration, p=0.044
	Most recent clinical visit (n=26)	4.40 (±2.20) compared with 3.50 (±1.53) at baseline Difference 0.90 (95% CI 0.45 to 1.36) Statistically significant deterioration, p<0.001 There was no deterioration in EDSS score in 13/26 patients (50.0%)
Adverse events	Treatment-emergent adverse events	16 events in 9/28 patients (32.1%)
	Serious treatment-emergent adverse events	16 events in 9/28 patients (32.1%)
	Treatment-related adverse events	0 events in any patients
[1] The Rankin scale is a tool used to measure the level of a person's neurological disability and dependence and ranges from 0 (perfect health without symptoms) to 6 (death) [2] The EDSS is a tool used to rate a person's level of neurological disability. It ranges from 0 to 10, with 0.5 unit increments representing higher levels of disability. 10 indicates death		
Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; p, p value; SD, standard deviation		

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Changes from baseline with chenodeoxycholic acid treatment		
Mean serum levels (micromol/litre) of cholestanol (SD)	Baseline	Elevated in all 14 patients (100%): mean 62 (25), range 20–98
	Within a few months	Levels became normal: 9 (4), range 2–16 Statistically significant improvement, p<0.001 Relapse was subsequently seen in 3 patients, linked to poor compliance with chenodeoxycholic acid
Mean EDSS score[1]	Baseline	Mean 3.0 (2.3), range 0–7.5

(SD)	Most recent clinical visit (mean follow-up 5 years)	Overall, mean EDSS remained stable: 3.4 (2.7), range 0–8) EDSS scores improved in 4 patients (28.6%), remained stable in 5 patients (35.7%) and worsened in 5 patients (35.7%) No statistical analyses were reported for this outcome The 3 people whose EDSS score worsened by at least 1 point had the longest time between experiencing their first cognitive and/or motor symptoms and starting treatment (25–32 years)
Mean SARA score[2] (SD)	Baseline	This score was assessed in only 6 people Mean 5.3 (3.9), range 1.5–12
	Most recent clinical visit (mean follow-up 5 years)	Mean 2.0 (1.4), range: 1–4 Statistically significant improvement, p=0.043 It is unclear if this 3 point improvement on a 40-point scale is clinically important
Electroneuromyography: mean dCMAP (m/s) (SD) and motor CV (m/s) (SD)	Baseline	11/13 patients had peripheral neuropathy[3]
	Most recent clinical visit (mean follow-up 5 years)	Mean dCMAP increased from 2.49 (1.65) to 3.57 (2.55) Statistically significant improvement, p=0.015 Mean CV increased from 33.8 (4.0) to 41.8 (4.2) Statistically significant improvement, p=0.002 It is unclear if these improvements are clinically important
Brain structure: volumetric analyses and DWI on MRI	Baseline	Before treatment, volumetric and DWI data were available for 6 and 8 patients respectively During the study, 11/14 patients (78.6%) were found to have brain atrophy on MRI
	After 3 years	Data were available for 4 patients only Volumetric analyses showed no overt volume loss DWI showed some improvements
Diarrhoea	Baseline	10/14 patients (71.4%) presented with infantile-onset diarrhoea
	Most recent clinical visit	Not reported
Xanthomas	Baseline	2/14 patients (14.2%) presented with xanthomas
	Most recent clinical visit	Not reported

Cataracts	Baseline	Not reported
	Most recent clinical visit	11/14 (78.6%) patients had surgery for a bilateral cataract
Cognitive impairment	Baseline	All 14 patients (100%) presented with cognitive dysfunction
	Most recent clinical visit	Not reported
Psychiatric impairment	Baseline	6/14 patients (42.9%) presented with psychiatric impairment
	Most recent clinical visit	Not reported
Adverse events		Tolerance to the drug was always good, including normal liver functions.
[1] The EDSS is a tool used to rate a person's level of neurological disability. It ranges from 0 to 10, with 0.5 unit increments representing higher levels of disability. 10 indicates death [2] The SARA is a tool used to assess and rate a person's level of ataxia. It ranges from 0 (no cerebellar symptoms) to 40 (most severe cerebellar symptoms). [3] 1 patient had electroneuromyography after receiving treatment for 9 months, which was normal		
Abbreviations: CV, conduction velocities (in nerves in muscle); dCMAP, distal compound muscle action potential (in nerves in muscle); DWI, diffusion weighted imaging; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; p, p value; 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.