MANAGEMENT IN CONFIDENCE

CLINICAL PRIORITIES ADVISORY GROUP
29 05 2019 and 30 05 2019

Agenda Item No	03.6
National Programme	Women and Children
Clinical Reference Group	Metabolic Disorders
URN	1623/96

Title
Cholic acid and chenodeoxycholic acid for treating inborn errors of bile acid synthesis (all ages)

Actions Requested	1. Support the policy proposition.
	2. Recommend the relative priority.

Proposition
This policy proposition is for routine commissioning. Inborn errors of bile acid synthesis are a group of very rare conditions (less than 65 known patients in England) where the liver has difficulty making important substances called bile acids (such as cholic acid and chenodeoxycholic acid). Untreated these diseases cause liver disease, cirrhosis (scarring of the liver), liver failure neurological diseases affecting movement and death. There are no curative treatments for these conditions. Cholic acid and chenodeoxycholic acid are the only treatments for these diseases and may be used singly or in combination. This policy document covers monotherapy and combination therapy in all ages.

Clinical Panel recommendation
The Clinical Panel recommended that the policy progress as a routine commissioning policy.

The committee is asked to receive the following assurance:	
1.	The Head of Clinical Effectiveness confirms the proposal has completed the appropriate sequence of governance steps and includes an: Evidence Review; Clinical Panel Report.
2.	The Head of Acute Programmes / Head of Mental Health Programme confirms the proposal is supported by an: Impact Assessment; Stakeholder Engagement Report; Consultation Report; Equality Impact and Assessment

	Report; Clinical Policy Proposition. The relevant National Programme of Care Board has approved these reports.
3.	The Director of Finance (Specialised Commissioning) confirms that the impact assessment has reasonably estimated a) the incremental cost and b) the budget impact of the proposal.
4.	The Clinical Programmes Director (Specialised Commissioning) confirms that the service and operational impacts have been completed.

The following documents are included (others available on request):	
1.	Clinical Policy Proposition
2.	Consultation Report
3.	Evidence Summary
4.	Clinical Panel Report
5.	Equality Impact and Assessment Report

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

The Benefits of the Proposition –		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	Survival was not measured, but the studies recorded deaths. The main study (Heubi et al. 2017) reported that 7 people died during treatment. Four people had end-stage liver disease at the start of treatment and became worse, and 3 people had worsening liver disease. Death was not thought to be related to cholic acid treatment. In the continuation study (study CAC-002-001, which reported combined results for 41 people with single enzyme deficiencies and peroxisomal disorders), 3 people died, 1 because of disease progression, 1 because of thrombosis (blood clots), and no cause was provided for the third person. None of the adverse events leading to death were thought to be related to cholic acid. Similar findings of low numbers of deaths were reported in another study. Results suggest that deaths were commonly reported because of the condition, and not because of treatment. The results above should be interpreted with caution as they are based on single armed studies. It means that they did not randomise patients (therefore they do not reduce the risk of other factors influencing the results) or compare the treatment with any other standard treatment (therefore they do not provide evidence that cholic acid is any better or worse than other treatments for this outcome, although there are limited

		alternative treatment options in clinical practice). It is not possible to determine what proportion of deaths are attributable to cholic acid treatment and what proportion are likely to be a direct consequence of the disease. Some people received additional treatment with ursodeoxycholic acid as well as cholic acid, which may disguise the true treatment effect of cholic acid. Some of the safety outcomes reported in the continuation study included people with another condition as well as single enzyme deficiency disorders which may have influenced the results.
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	
8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	<u>Adverse events related to treatment</u> In the main study with 54 people with single enzyme deficiencies, 3 adverse events were considered related to treatment: malaise (weakness) and jaundice (yellowing if the skin) in 1 person, and skin lesions in another person, which were not thought to be serious. In the continuation of the main study, 2 adverse events were considered related to treatment: peripheral neuropathy (nerve damage in areas such as the hands, feet and arms) in 1 person and nausea in another, both reported to be of a mild nature that resolved. These results suggest that some people who take cholic acid may experience adverse events related to cholic acid treatment. <u>Serious adverse events</u> The main study reported 6 serious adverse events in 5 people. The most frequently reported serious adverse event was disease progression. This was followed by diarrhoea, urinary tract infection and dehydration. These were not thought to be related to treatment. One study (Gonzales et al. 2009) reported an accidental overdose that caused pruritis (itching of the skin),

		diarrhoea, and a short-term increase in particular liver function tests. These symptoms resolved after reducing dose. Results suggest that some people with the condition may be at risk of a serious adverse event that is more likely to be related to their condition rather than cholic acid treatment. <u>Stopping treatment with cholic acid</u> The main study reported that 3 people stopped taking cholic acid. The most common reason was because of disease progression and was not thought to be related to treatment. In the continuation study, 4 people stopped taking cholic acid (3 because of disease progression, and 1 because of peripheral neuropathy). Results suggest only a few people stopped taking cholic acid treatment, usually because of their condition getting worse. All results above should be interpreted with caution as they are based on single armed studies. It means that they did not randomise patients (therefore they do not reduce the risk of other factors influencing the results) or compare the treatment with any other standard treatment (therefore they do not provide evidence that cholic acid is any better or worse than other treatments for this outcome), although there are limited alternative treatment options in clinical practice). It is not possible to determine what proportion of side effects are attributable to cholic acid treatment and what proportion are likely to be a direct consequence of the disease. Some people received additional treatment with ursodeoxycholic acid as well as cholic acid, which may disguise the true treatment effect of cholic acid. Some of the safety outcomes reported in the continuation study included people with another condition as well as single enzyme deficiency disorders which may have influenced the results.
11.	Delivery of intervention	

Other health outcome measures determined by the evidence review		
No	*Outcome measure*	*Summary from evidence review*
1.	Abnormal urinary bile acids	This outcome compared the average level of abnormal bile acids (produced by the body as a result of the condition) in people’s urine before and after cholic acid to see if treatment reduced the amount.

		The main study (Heubi et al. 2017, n=54), found a statistically significant reduction in the percentage of people with abnormal urinary bile acids after treatment compared with before, over an 18-year period. Similar results were shown in supporting studies and the literature review of smaller studies from the European public assessment reports (EPAR). Results suggest treatment with cholic acid may reduce abnormal urinary bile acids in people with inborn errors of primary bile acid synthesis, indicating a reduction in the production of toxic bile acids that can have an adverse effect on the liver. Results should be interpreted with caution as they are based on a single arm study. It means that it did not randomise patients (therefore it does not reduce the risk of other factors influencing the results) or compare the treatment with any other standard treatment (therefore it does not provide evidence that cholic acid is any better or worse than other treatments for this outcome, although there are limited alternative treatment options in clinical practice). Some people received additional treatment with ursodeoxycholic acid as well as cholic acid, which may disguise the true treatment effect of cholic acid. Cholic acid is licensed for 5 different subtypes of inborn error of bile acid synthesis, but results were not generally reported by subtype, and the subtypes had uneven representation across and within studies.
2.	Liver function	This outcome compared levels of liver enzymes in blood before and after treatment, which can show if liver function improved with cholic acid treatment. The main study (Heubi et al. 2017, n=54) found statistically significant improvements in the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) after treatment compared with before treatment. Similar results were shown in supporting studies and the literature review of smaller studies from the EPARs. Results suggest treatment with cholic acid may improve liver function in people with inborn errors of primary bile acid synthesis. Please see last paragraph in ‘Summary from evidence review’ for metric 1 – Abnormal urinary bile acids for a commentary on uncertainties of evidence from Heubi et al. 2017.

3.	Height and weight	Inborn errors of primary bile acid synthesis affect the absorption of fat and fat-soluble vitamins in the intestines, which can affect growth. This outcome compared height and weight before and after treatment with cholic acid. The main study (Heubi et al. 2017, n=54) found an increase in height and weight percentiles after treatment compared with before treatment. However, statistical significance was shown only for the change in weight. Similar increase in height and weight were reported in the other studies. Results suggest treatment with cholic acid may help to improve growth in people with inborn errors of primary bile acid synthesis. Please see last paragraph in 'Summary from evidence review' for metric 1 – Abnormal urinary bile acids for a commentary on uncertainties of evidence from Heubi et al. 2017.
4.	Clinical features	People with inborn errors of primary bile acid synthesis may present with some common symptoms (or clinical features) associated with the condition, such as fatty stools, enlarged liver or absent tendon reflexes. This outcome compared clinical features before and after treatment. This outcome was reported by Gonzales et al. 2009 (15 people with 3beta-HSD deficiency and 5beta-reductase deficiency). The number of people with an enlarged liver, fatty stools, and absent tendon reflexes reduced from 15, 13, and 7 people before treatment to 4, 9, and 3 people respectively after 5 years of treatment. Statistical significance was reported for the symptom fatty stools. Results suggest treatment with cholic acid may improve some of the clinical features in people with inborn errors of primary bile acid synthesis. The uncertainties of the evidence for this outcome were the same as that for Heubi et al. 2017. Please see last paragraph in 'Summary from evidence review' for metric 1 – Abnormal urinary bile acids for a commentary on uncertainties of evidence from Heubi et al. 2017.
5.	Response to cholic acid treatment	People with inborn errors of primary bile acid synthesis accumulate toxic substances because of reduced flow of bile acid and this can result in reduced flow of bile from the liver (cholestasis), the liver not functioning as it should do (liver dysfunction), liver failure and death due to disease progression. This outcome is a measure of how long after starting cholic acid treatment people with the condition are

		expected to see an improvement in cholestasis and liver dysfunction, and also how many people survived with their own liver. Al Hussaini et al. 2017 n= 15) found that 11 people were reported to survive after a median follow-up of 4.5 years; 10 of these had their own liver and 1 had a liver transplant 2 months after starting treatment with cholic acid. Cholestasis was reported to improve, but no numerical data were given. Liver dysfunction was not clearly reported in the study. It was unclear from this study whether treatment with cholic acid affected survival and the need for a liver transplant because there was no control to compare this with. As there was no numerical data provided in the study, it is not known if treatment with cholic acid affected cholestasis and liver dysfunction. The uncertainties of the evidence for this outcome were the same as that for Heubi et al. 2017. Please see last paragraph in 'Summary from evidence review' for metric 1 – Abnormal urinary bile acids for a commentary on uncertainties of evidence from Heubi et al. 2017. In addition, the study did not provide a clear definition of what was meant by the term 'improved' which made it difficult to assess the clinical importance of it.

B Clinical evidence review of chenodeoxycholic acid for treating cerebrotendinous xanthomatosis

The Benefits of the Proposition		
No	*Outcome measures*	*Summary from evidence review*
1.	Survival	
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	

8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	Treatment-*emergent* adverse events are undesirable events that were either not present before treatment, or present but which worsened after treatment. They may or may not be associated with treatment. Treatment-*related* adverse events are those considered related to the treatment being investigated. In the main study, CDCA-STUK-15-001 (n=35), 76 treatment-emergent adverse events were reported in 26/35 people (74.3%). 9/76 treatment-emergent adverse events in 7 people were considered serious. 3 were considered related to chenodeoxycholic acid treatment (constipation in 2 people and toxic hepatitis in 1 person, not thought to be serious). There were 16 treatment-emergent adverse events in 9/28 people (32.1%) in the supportive study, CDCA-STRCH-CR-14-001 (n=28), all considered serious, none treatment-related. Treatment was 'well tolerated' in del Mar Amador et al. (n=14). In summary, adverse events were generally not serious, and mostly related to underlying disease, rather than treatment. Results should be interpreted with caution because studies are small (n=35, n=28 and n=14), uncontrolled, and retrospective. 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. Weaknesses in the studies' design and conduct mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions.
11.	Delivery of intervention	

Other health outcome measures determined by the evidence review		
No	*Outcome measure*	*Summary from evidence review*
1.	Serum cholestanol levels	Cholestanol is a substance in the body, which can build up in people with CTX and damage organs. This outcome compared average levels before and after

		chenodeoxycholic acid to see if treatment reduced the amount. The main study, CDCA-STUK-15-001 (n=35), found a statistically significant reduction at 3 different time points compared with pre-treatment levels. At the most recent clinical visit (on average about 10 years' after treatment), cholestanol reduced by 63 micromol/litre compared with baseline (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 the supportive studies and the European public assessment report (EPAR) (n=174). Results suggest chenodeoxycholic acid may reduce serum levels of cholestanol, reducing the risk of organ damage. Please see last paragraph in 'Summary from evidence review' for metric 10 – Safety for a commentary on uncertainties of evidence from CDCA-STUK-15-001, CDCA-STRCH-CR-14-001 and del Mar Amador et al.
2.	Urinary bile alcohol levels	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 before and after chenodeoxycholic acid to see if treatment reduced the amount. The main study, CDCA-STUK-15-001 (n=35), 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. 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. Please see last paragraph in 'Summary from evidence review' for metric 10 – Safety for a commentary on uncertainties of evidence from CDCA-STUK-15-001.

3.	Diarrhoea	This outcome compared the number of people with diarrhoea before and after treatment. In the main study, CDCA-STUK-15-001 (n=35), 23/31 people [74%] had this symptom at baseline, and it resolved by the most recent clinical visit in all 23 people. Similar results were seen in the literature review in the EPAR. However, in the supportive study, CDCA-STRCH-CR-14-001 (n=28), 11/26 people (42%) still had diarrhoea at the most recent clinical visit. Note that people in the supportive study were, on average, older (mean age 35 years compared with 26 years in the main study) and had higher disability scores at baseline. Results suggest 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. Please see last paragraph in 'Summary from evidence review' for metric 10 – Safety for a commentary on uncertainties of evidence from CDCA-STUK-15-001 and CDCA-STRCH-CR-14-001.
4.	Xanthomata	Xanthomata are fatty deposits around the tendons. This outcome compared the number of people with xanthomata before and after chenodeoxycholic acid to see if treatment reduced this symptom. The main study, CDCA-STUK-15-001 (n=35), 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 whether xanthomas improved, stabilised or deteriorated. The supportive study, CDCA-STRCH-CR-14-001 (n=28), reported xanthomata 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 chenodeoxycholic acid has no protective effect on the incidence of xanthomata, although it may help to improve or stabilise xanthomas in some people who currently have these. Please see last paragraph in 'Summary from evidence review' for metric 10 – Safety for a commentary on uncertainties of evidence from CDCA-STUK-15-001 and CDCA-STRCH-CR-14-001.
5.	Cataracts	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 the main study, CDCA-STUK-15-001 (n=35), 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 the supportive study, CDCA-STRCH-CR-14-001 (n=28), 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. Please see last paragraph in 'Summary from evidence review' for metric 10 – Safety for a commentary on uncertainties of evidence from CDCA-STUK-15-001 and CDCA-STRCH-CR-14-001.
6.	Cognitive impairment	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 the main study, CDCA-STUK-15-001 (n=35), 18/31 people (58%) had cognitive impairment at baseline. 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 EPAR (n=35). By contrast, in the supportive study, CDCA-STRCH-CR-14-001 (n=28), 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 the main study, with a younger population (mean age 26 years) who were at an earlier stage of disease. By contrast, in the supportive study, 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. Please see last paragraph in 'Summary from evidence review' for metric 10 – Safety for a commentary on uncertainties of evidence from CDCA-STUK-15-001 and CDCA-STRCH-CR-14-001.Also, there is little information

		available about what the broad term ‘cognitive impairment’ includes.
7.	Psychiatric impairment	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 the main study, CDCA-STUK-15-001 (n=35), 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 the supportive study, CDCA-STRCH-CR-14-001 (n=28), 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. Please see last paragraph in ‘Summary from evidence review’ for metric 10 – Safety for a commentary on uncertainties of evidence from CDCA-STUK-15-001 and CDCA-STRCH-CR-14-001.Also, there is little information available about what the broad term ‘psychiatric impairment’ includes.
8.	Neurological impairment	This outcome compared the number of people with neurological impairment before and after chenodeoxycholic acid to see if treatment reduced this symptom. In the main study, CDCA-STUK-15-001 (n=35), 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 the supportive study, CDCA-STRCH-CR-14-001 (n=28), got worse in spite of treatment. 26/97 people (29%) got worse in the literature review in the EPAR (n=97). Neuropathy was assessed by measuring how well the nerves conduct signals in the study by del Mar Amador et al. (n=14) and, overall, significant improvements were seen with chenodeoxycholic acid. In summary, in the main study 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 the supportive study 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. Please see last paragraph in 'Summary from evidence review' for metric 10 – Safety for a commentary on uncertainties of evidence from CDCA-STUK-15-001, CDCA-STRCH-CR-14-001 and del Mar Amador et al.
9.	Neurological disability measured using the Rankin Scale score	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 the main study, CDCA-STUK-15-001 (n=35), 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 significant. Results of the supportive study, CDCA-STRCH-CR-14-001 (n=28), were generally similar although Rankin scores worsened in a higher proportion of people than in the main study, and the overall deterioration in scores was statistically significant at 2 out of 3 time points. Note that people in the supportive study 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. Please see last paragraph in 'Summary from evidence review' for metric 10 – Safety for a commentary on uncertainties of evidence from CDCA-STUK-15-001 and CDCA-STRCH-CR-14-001.
10.	Neurological disability measured using the Expanded Disability Status Scale (EDSS)	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 the main study, CDCA-STUK-15-001 (n=35), 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 the supportive study, CDCA-STRCH-CR-14-001 (n=28), were generally similar although EDSS scores worsened in a higher proportion of people than in the main study, and the overall deterioration in scores was statistically significant at all time points. Note that people in the supportive study were, on average, older and had higher disability scores at baseline. Similar results were seen in the study by del Mar Amador et al. (n=14) 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. Please see last paragraph in 'Summary from evidence review' for metric 10 – Safety for a commentary on uncertainties of evidence from CDCA-STUK-15-001, CDCA-STRCH-CR-14-001 and del Mar Amador et al.

C Cholic acid and chenodeoxycholic acid for inborn errors of primary bile acid synthesis

The Benefits of the Proposition – Cholic acid and chenodeoxycholic acid for inborn errors of primary bile acid synthesis		
No	*Metric*	*Summary from evidence review*
1.	Survival	
2.	Progression free survival	
3.	Mobility	
4.	Self-care	
5.	Usual activities	
6.	Pain	
7.	Anxiety / Depression	

8.	Replacement of more toxic treatment	
9.	Dependency on care giver / supporting independence	
10.	Safety	
11.	Delivery of intervention	

Other health metrics determined by the evidence review: Cholic acid and chenodeoxycholic acid for inborn errors of primary bile acid synthesis		
No	Metric	Summary from evidence review
1.	Liver function	Liver function tests are blood tests which indicate how well the liver is performing some of its functions. Lemonde et al (2003)'s reported results following the introduction of cholic acid and chenodeoxycholic acid in two infants with Δ4-3-oxosteroid 5β-reductase deficiency and a *SRD5B1* gene mutation. The first infant presented at 3 weeks with bilirubin 316 μmol/l (conjugated 145), AST 2279 U/l, ALT 1123 U/l and prothrombin time 15.4 seconds (control 12) (normal ranges were not stated). This infant was treated at 3 months of age with ursodeoxycholic acid and continued to have steatorrhoea, failure to thrive and fat soluble vitamin malabsorption. At an unspecified time at or after 8 months of age, treatment was changed to CA (8mg/kg/day) and CDCA (8mg/kg/day). Results probably before the introduction of CA plus CDCA (though the authors do not state this), were bilirubin 88 μmol/l, AST 511 U/l, ALT 252 U/l, γ-GT 36 U/l. The authors do not state normal ranges but indicate that the first three results were elevated while the γ-GT was normal. Other results for this infant were CDCA (normal range 0.2 to 12.7 μmol/l) <0.05 μmol/l; CA (normal range 0.4 to 6.7 μmol/l) <0.05 μmol/l; 7α-hydroxy-3-oxo-4-cholenoic acid (normal range <0.05 μmol/l) 1.9 μmol/l; 7α,12α-dihydroxy-3-oxo-4-cholenoic acid (normal range <0.05 μmol/l) 2.1 μmol/l. There are no reported results for this infant after treatment, though it "led to normalisation of liver function within three months and she remains well with normal liver function tests at the age of nine years (on bile acid replacement therapy)."

		The second infant was treated from eight weeks of age with CA plus CDCA. Pre-treatment results included bilirubin 446 µmol/l (normal range not reported), alanine transaminase (normal range 5 to 45 U/l) 1702 U/l and γ-glutamyl transaminase (normal range 20 to 155 U/l) 103 U/l. After 6 weeks of treatment, results were bilirubin 117 µmol/l, alanine transaminase 184 U/l and γ-glutamyl transaminase 243 U/l. However, the authors report no tests of statistical significance. The infant had a successful liver transplant. These results are consistent with an improvement in liver function. However, the impact of improvements in liver function tests of these magnitudes cannot be assessed, as such results are not directly related to improvements in patients' symptoms, ability to carry out activities, quality of life, disease progression and survival. The clinical benefit to patients from the use of cholic acid and chenodeoxycholic acid cannot be estimated from this study. Fluctuations in the patients' clinical status or the play of chance are alternative explanations, particularly when so few patients are reported. Furthermore, bile acids are part of several biochemically distinct pathways and disorders of bile acid synthesis have variable effects. It is difficult to apply the findings more widely of one study of a specific gene defect.
2.	Urinary bile acid concentrations	Urinary bile acid concentrations reflect the presence in the urine and blood of bile acids given as treatment or potentially influenced by treatment, and may indicate how well the liver is performing some of its functions. A reduction in concentrations of abnormal urinary bile acids is consistent with improvements in liver function. Clayton et al 2003 reported results following the introduction of cholic acid and chenodeoxycholic acid in a child with Δ4-3-oxosteroid 5β-reductase deficiency. Urinary excretion of 7α-hydroxy-3-oxo-4-cholenoic acid on no treatment was 22 µmol/mmol creatinine, on ursodeoxycholic acid it was 9.1 µmol/mmol creatinine, and on cholic acid and chenodeoxycholic acid it was 1 µmol/mmol creatinine (normal ranges not reported). Urinary excretion of 7α,12α-dihydroxy-3-oxo-4-cholenoic acid on no treatment was 94 µmol/mmol creatinine, on ursodeoxycholic acid it was 82 µmol/mmol creatinine, and on cholic acid and chenodeoxycholic acid it was 22 µmol/mmol creatinine (normal ranges not reported). However, the authors report no tests of statistical significance. These results are consistent with an improvement in liver function. However, the impact of improvements in bile acid

		excretion of these magnitudes cannot be assessed, as such results are not directly related to improvements in patients' symptoms, ability to carry out activities, quality of life, disease progression and survival. The clinical benefit to patients from the use of cholic acid and chenodeoxycholic acid cannot be estimated from this study. Fluctuations in the patients' clinical status or the play of chance are alternative explanations, particularly when so few patients are reported. Furthermore, bile acids are part of several biochemically distinct pathways and disorders of bile acid synthesis have variable effects. It is difficult to apply the findings more widely of one study of a specific biochemical defect in one child, especially one in which the authors note that "The plasma bile acid profile of the patient was unique", limiting the generalisability of this study.

Considerations from review by Rare Disease Advisory Group
Not applicable.

Pharmaceutical considerations
This policy recommends cholic acid (2 branded products with slightly different licenses) and chenodeoxycholic acid within their approved Marketing Authorisations and in combination outside of its licensed indications which constitutes an off label use of these drugs. The policy also allows for off label use of individual cholic acid products for which they are not individually licensed. Both are excluded from tariff.

Considerations from review by National Programme of Care
The proposal received the full support of the Women and Children's Programme of Care Board on 25th April 2019.