Assessment report

Chenodeoxycholic acid sigma-tau

International non-proprietary name: chenodeoxycholic acid

Procedure No. EMEA/H/C/004061/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.
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<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<tr>
<td>ALT</td>
<td>Alanine Aminotransferase</td>
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<tr>
<td>AST</td>
<td>Aspartate Aminotransferase</td>
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<tr>
<td>ATC</td>
<td>Anatomic Therapeutic Chemical classification system</td>
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<tr>
<td>BUN</td>
<td>Blood Urea Nitrogen</td>
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<tr>
<td>CA</td>
<td>Cholic acid</td>
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<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
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<tr>
<td>CDCA</td>
<td>Chenodeoxycholic acid</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<td>CPK</td>
<td>Creatine Phosphokinase</td>
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<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>CS</td>
<td>Clinically Significant</td>
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<tr>
<td>CSF</td>
<td>Cerebrospinal Fluid</td>
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<tr>
<td>CT</td>
<td>Computerised Tomography</td>
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<tr>
<td>CTCAE</td>
<td>Common Toxicity Criteria for Adverse Event</td>
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<td>CTX</td>
<td>Cerebrotendinous Xanthomatosis</td>
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<tr>
<td>DCA</td>
<td>Deoxycholic acid</td>
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<tr>
<td>EDSS</td>
<td>Expanded Disability Status Scale</td>
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<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
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<tr>
<td>EMG</td>
<td>Electromyography</td>
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<tr>
<td>FLAIR</td>
<td>Fluid Attenuation Inversion Recovery</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>HMG-CoA</td>
<td>3-Hydroxy-3-Methylglutaril-CoA</td>
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<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
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<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<td>IEC</td>
<td>Independent Ethic Committee</td>
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<tr>
<td>LCA</td>
<td>Lithocholic acid</td>
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<tr>
<td>LDH</td>
<td>Lactic Dehydrogenase</td>
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<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
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<tr>
<td>MEPs</td>
<td>Motor Evoked Potentials</td>
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<td>MMRM</td>
<td>Mixed Model for Repeated Measures</td>
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<td>MMSE</td>
<td>Mini Mental State Examination</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>NCS</td>
<td>Non-clinically Significant</td>
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<tr>
<td>PT</td>
<td>Preferred Term</td>
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<tr>
<td>PTH</td>
<td>Parathyroid Hormone</td>
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<tr>
<td>RBC</td>
<td>Red Blood Cell</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAP</td>
<td>Statistical Analysis Plan</td>
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<td>SAS</td>
<td>Statistical Analysis System</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SI</td>
<td>International System of Units</td>
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<tr>
<td>SOC</td>
<td>System Organ Class</td>
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<tr>
<td>UDCA</td>
<td>Ursodeoxycholic acid</td>
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<tr>
<td>WBC</td>
<td>White Blood Cell</td>
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<tr>
<td>WHO-DD</td>
<td>World Health Organization-Drug Dictionary</td>
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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Sigma-tau Arzneimittel GmbH submitted on 14 September 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Chenodeoxycholic acid sigma-tau, through the centralised procedure under Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 May 2015.

The application concerns a hybrid medicinal product as defined in Article 10(3) of Directive 2001/83/EC and refers to a reference medicinal product for which a marketing authorisation is or has been granted in a Member State on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

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

Chenodeoxycholic acid sigma-tau was designated as an orphan medicinal product EU/3/14/1406 on 16 December 2014. Chenodeoxycholic acid sigma-tau was designated as an orphan medicinal product in the following indication:

Treatment of inborn errors of primary bile acid synthesis.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Chenodeoxycholic acid sigma-tau as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designations.

The legal basis for this application refers to:

Hybrid application (Article 10(3) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and literature references with the medicinal product Xenbilox.

Information on paediatric requirements

Not applicable. Paediatric requirements, as described in Regulation (EC) No 1901/2006, do not apply for medicinal products under Article 10(3) of Directive 2001/83/EC – hybrid application.
**Information relating to orphan market exclusivity**

**Similarity**

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products for a condition related to the proposed indication.

The chosen reference medicinal product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Xenbilox, 250mg, capsules, hard
- Marketing authorisation holder: Sigma-Tau Rare Disease Ltd.
- Date of authorisation: 13 September 1999
- Marketing authorisation granted by:
  - Member State (EEA) : Germany
  - National procedure
- Marketing authorisation number: 6293321.00.00

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Xenbilox, 250mg, capsules, hard
- Marketing authorisation holder: Sigma-Tau Rare Disease Ltd.
- Date of authorisation: 13 September 1999
- Marketing authorisation granted by:
  - Member State (EEA) : Germany
  - National procedure
- Marketing authorisation number: 6293321.00.00
Applicant’s request for consideration

Marketing Authorisation under exceptional circumstances

The applicant provided a justification for its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004 based on the following claims: the applicant justified that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because: the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, and that it would be contrary to generally accepted principles of medical ethics to collect such information.

The applicant proposed as specific obligation to expand the data available and collect long-term data on the clinical safety and efficacy of chenodeoxycholic acid in the treatment cerebrotendinous xanthomatosis by establishing a patient database.

Protocol assistance

The applicant did not seek protocol assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Robert James Hemmings  Co-Rapporteur: George Aislaitner

• The application was received by the EMA on 14 September 2015.

• The procedure started on 29 October 2015.

• The Rapporteur’s first Assessment Report was circulated to all CHMP members on 15 January 2016. The PRAC Rapporteur’s first Assessment Report was circulated to all PRAC members on 19 January 2016.

• During the meeting on 11 February 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 12 February 2016.

• During the meeting on 25 February 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 February 2016.

• The applicant submitted the responses to the CHMP consolidated List of Questions on 29 March 2016.

• The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 18 April 2016.

• During the CHMP meeting on 28 April 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.

• The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues
on 20 June 2016.

- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 7 July 2016.

- During the CHMP meeting on 21 July 2016, the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant.

- The applicant submitted the responses to the CHMP consolidated Second List of Outstanding Issues on 16 August 2016.

- The Rapporteur circulated the Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 31 August 2016.

- During the meeting on 15 September 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation under exceptional circumstances to Chenodeoxycholic acid sigma-tau.

- The CHMP adopted a report on similarity of Chenodeoxycholic acid sigma-tau with authorised orphan medicinal products on 15 September 2016.

2. Scientific discussion

2.1. Introduction

Problem statement
The inborn errors of bile acid synthesis are a category of metabolic liver diseases (Setchell & Heubi, 2006). These conditions are extremely rare genetic disorders. Individuals with inborn errors of bile acid synthesis lack the enzymes needed to synthesize the primary bile acids. This deficiency in activity of specific enzymes results in diminished production of primary bile and the concomitant production of high concentrations of atypical bile acids and bile acid intermediates (Heubi et al., 2007). The absence of primary bile acids causes hepatocytes to continuously metabolize cholesterol in an attempt to establish normal bile acid pool. The result is the continued production of high concentrations of hepatotoxic metabolites, which cause a progressive cholestasis.

Cerebrotendinous xanthomatosis (CTX; OMIM 213700) is an autosomal recessive lipid storage disease caused by disruption of bile acid synthesis that was first described in 1937. A deficiency of the enzyme sterol 27-hydroxylase causes the accumulation of cholesterol and cholestanol in virtually all tissues (Federico 2013, Skrede 1985). Fat deposition leads to the formation of xanthomas, nodules, and plaques in the central nervous system, tendons, skin, lungs, and bones.

CTX is one of a group of neurologic disorders, collectively referred to as leukodystrophies, which predominantly affect the central nervous system white matter. These disorders are caused by defects in the synthesis or maintenance of the myelin sheath that insulates the nerves. The main neurologic features of CTX are cerebellar ataxia, pyramidal tract signs, and intellectual decline. One or more of these is usually apparent by late childhood or early adulthood. The syndrome is slowly progressive, and while there is no cure, its course can be altered with treatment.

About the product
Chenodeoxycholic acid (CDCA) is one of the five major bile acids in humans. The others are deoxycholic acid (DCA), cholic acid (CA), ursodeoxycholic acid (UDCA), and lithocholic acid (LCA). Bile acids are composed of four steroid rings forming a hydrocarbon lattice with a convex hydrophobic (β face) face and a concave hydrophilic (α face). This amphipathic structure gives the detergent properties to bile acid and allows for lipid and fat-soluble vitamin absorption from the small intestine.

**Type of Application and aspects on development**

This application is submitted under Article 10(3) of Directive 2001/83/EC ("hybrid“ Application) using Xenbilox as reference medicinal product and is supported by clinical data and literature review. The applicant did not conduct any clinical studies against the reference medicinal product, which was justified by the differences in the indication. The application for Chenodeoxycholic acid sigma tau only referred in certain areas to Xenbilox and in all these areas there was no need for bioequivalence or comparable bioavailability studies to the reference medicinal product.

In accordance with Article 14(8) of Regulation (EC) No 726/2004 and Annex I, part II of the Directive 2001/83/EC the applicant applied for a marketing authorisation under exceptional circumstances. The applicant argued that he was unable to provide comprehensive data on the efficacy and safety under normal conditions of use because the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, and that it would be contrary to generally accepted principles of medical ethics to collect such information.

**2.2. Quality aspects**

**2.2.1. Introduction**

The finished product is presented as hard capsules containing 250 mg of chenodeoxycholic acid as active substance.

Other ingredients are:

- **Capsule content**: maize starch, magnesium stearate, silica, colloidal anhydrous, and water
- **Capsule shell**: gelatine, titanium dioxide (E 171), quinoline yellow (E 104), and erythrosine (E 127)

The product is available in polyvinyl chloride (PVC) blisters sealed with aluminium foil as described in section 6.5 of the SmPC.

**2.2.2. Active substance**

**General information**

The chemical name of chenodeoxycholic acid is 3α,7α-dihydroxy-5β-cholan-24-oic acid corresponding to the molecular formula C_{24}H_{40}O_{4}. It has a relative molecular mass of 392.56 g/mol and the following structure:
The structure was determined by elemental analysis, $^1$H-NMR, $^{13}$C-NMR, $^{13}$C DEPT NMR, mass spectrometry, IR spectroscopy and X-ray diffraction.

The active substance is a white crystalline powder that may absorb humidity from atmosphere, and is soluble in methyl alcohol, ethyl alcohol, in acetone, in glacial acetic acid and in dilute aqueous solutions of alkali hydroxides. It is weakly soluble in ether and ethyl acetate. It is insoluble in water, in petrol ether and in benzene.

Different crystalline polymorphic forms have been observed. The form manufactured by the proposed manufacturer is form I which is known to be stable from published literature.

**Manufacture, characterisation and process controls**

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packed in a low density polyethylene double bag as primary packaging and in a fibre drum as secondary packaging.

**Specification**

The active substance specification includes tests for appearance (Ph. Eur.), solubility (Ph. Eur.), identification (IR, TLC), specific optical rotation (Ph. Eur.), related substances (HPLC), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), loss on drying (Ph. Eur.), assay (HPLC), melting range, hydrazine, particle size (Ph. Eur.), polymorph I (X-ray diffraction), microbiological controls (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis data from 6 production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.
**Stability**

Stability data on 5 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions at 25 °C / 60% RH and for up to 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines were provided.

The parameters tested were appearance, assay, loss on drying, and related substances. Thus far, related substances have been quantified by TLC, but a more accurate HPLC method will be used from now on as requested by the CHMP. The HPLC method will also be used to measure assay (previously determined via acid-base determination) henceforward. So far the new HPLC method has only been used to measure long term stability data from one batch for up 12 months. Data on two additional batches for up to 12 months has been requested by CHMP. Full compliance with the proposed specification was reported, with no significant degradation detected under long term and accelerated conditions. The polymorphic form of batches was also tested at either 18 or 24 months by XRD. Results indicated that form 1 is stable during storage.

Photostability testing following the ICH guideline Q1B was performed on one batch. The stability data provided shows that the active substance is not affected by exposure to light.

Forced degradation studies under stressed conditions (acidic conditions (10% sol in HCl 1 N for 72 hours), basic conditions (10% sol in NaOH 1 N), oxidising conditions (5% sol in 2-8% hydrogen peroxide for 72 hours, heat (130°C)) were also provided on 1 batch. These results provided evidence that the substance does not show significant degradation under alkaline, acidic or oxidising conditions but and is adversely impacted by the exposure to heating at 130°C.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months without special storage conditions when it is stored in the proposed container. However, the CHMP recommended testing the active substance prior to use in finished product manufacturing, until results at the 12 month time point using the new HPLC method for the three batches become available. This data should be submitted through the relevant variation procedure.

**2.2.3. Finished medicinal product**

**Description of the product and Pharmaceutical development**

The finished product is presented as powder filled hard capsules with a yellow body and orange cap, containing a white, compressed powder.

Chenodeoxycholic acid capsules were developed in the 70s and acquired by the applicant at later stage. They have therefore been on the market for many years. However, this product has a different indication (orphan) from other products containing chenodeoxycholic acid which are authorised.

The aim of pharmaceutical development was to develop an immediate release capsule as it is considered the most appropriate dosage form for chenodeoxycholic acid and the proposed route of administration (oral use). During evaluation, it was considered that the proposed capsules were not suitable for use in children as they failed to allow the correct posology and also present a choking hazard. Therefore, the CHMP recommended developing an age appropriate pharmaceutical form for children or adults who cannot swallow the capsules. In the meantime, the product information was updated to include a description of the preparation and administration of a suspension to infants,
children, and adults who cannot swallow the capsules. The capsules may be carefully opened and the content added to sodium bicarbonate solution 8.4%. Step by step instructions are provided in the product information. The use of sodium bicarbonate as a suspending agent has been adequately justified and suspensions have been shown to be stable for up to 7 days. It is recommended that the suspension is prepared in a pharmacy and that an oral dosage syringe is provided for administration of the correct dose.

Chenodeoxycholic acid is an organic acid. It is relatively insensitive to the influence of oxygen, light, humidity and temperature. The free acid is lipophilic and poorly soluble in water. At pH 7 the substance goes into solution slowly. It dissolves quickly forming the corresponding salt (depending on the base used) at pH values exceeding 8.

The finished product is formulated from pharmacopoeial grade excipients commonly used for pharmaceutical presentations. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report. The specific excipients were chosen for their known functions and comprise maize starch (binding agent), magnesium stearate (lubricant) and colloidal anhydrous silica (disintegrant and anti-adhesive).

Different formulations were prepared and investigated during development which involved assessing the disintegration time and dissolution profile of granules manufactured with a varying amount of binding agent and granules manufactured with addition of various excipients. The formulation with the optimal disintegration time and dissolution rate proved to be the one containing the smallest amount of binding agent. This formulation was subsequently granulated and put into hard gelatin capsules by a standard manufacturing procedure without any problems occurring. The release of active ingredient proved to be rapid and nearly complete within 30 minutes using the chosen dissolution conditions. It is concluded that the formulation obtained with the chosen excipients is a product suitable for the intended purpose.

Differences between the clinical and proposed commercial formulations have negligible impact on the release properties of the finished product.

The proposed manufacturing process of wet granulation and tray drying is considered a standard manufacturing process. Therefore no extensive development of the manufacturing process took place.

The primary packaging is PVC blisters sealed with aluminium foil. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

**Manufacture of the product and process controls**

The manufacturing process consists of 8 main steps: weighing materials, preparation of granulation solution, granulation, mixing, pre-compression, trituration and final mixing, encapsulation, blister packaging, and secondary packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.
Product specification

The finished product release specifications re-produced below include appropriate tests for this kind of dosage form: appearance, disintegration time (Ph. Eur.), uniformity of dosage units (Ph. Eur.), identity of the active substance (HPLC, TLC), purity (HPLC), assay (HPLC), dissolution (Ph. Eur.), and microbial purity (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released onto the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored under long term conditions for up to 26 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches used in the stability studies are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, two batches were manufactured by the manufacturing process minus the pre-compression step. This manufacturing process is considered to be highly comparable to the proposed manufacturing process. Therefore stability data from these batches are supportive in providing relevant evidence on final product stability parameters. For these batches, stability data for 36 and 24 months respectively under long term conditions have been provided. In addition, data from one batch used in a bulk hold study was provided.

Samples were tested for appearance, disintegration time, uniformity of dosage units, purity, assay, dissolution and microbiological attributes. The analytical procedures used are stability indicating.

All the results complied with the shelf-life specification and no significant changes any of the measured parameters were observed.

As requested by CHMP, updated stability results were provided using the new HPLC method for purity testing at the last two points of the long term conditions stability study after 23 and 25 months for one batch and after 20 and 22 months for another batch. Considering the results obtained and the fact that purity after storage under accelerated conditions was not measured by HPLC, it was agreed that a shelf-life based only on long term stability data with no extrapolation based on accelerated data could be accepted in this instance.

Based on available stability data, the proposed shelf-life of 22 months with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

Gelatine obtained from bovine sources is used in the product. The gelatin used meets the criteria as described in the current version of the European pharmacopoeia monograph ‘Products with risk of transmitting agents of animal spongiform encephalopathies’.
Chenodeoxycholic Acid is a bile acid originating from cholic Acid that is extracted from ox gall. The origin countries are based on Resolution No.18, 82nd General Session, May 2014 and the classification according to OIE rules (referred to in the TSE Note for Guidance EMA/410/01 Rev. 3) and the last GBR classification.

2.2.4. **Discussion on chemical, and pharmaceutical aspects**

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. **Conclusions on the chemical, pharmaceutical and biological aspects**

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. **Recommendation(s) for future quality development**

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- To test the active substance prior to use in finished product manufacturing, until results at the 12 month time point using the new HPLC method for the three batches become available. This data should be submitted through the relevant variation procedure.

- To develop an age appropriate pharmaceutical form for children or adults that cannot swallow the capsules.

2.3. **Non-clinical aspects**

2.3.1. **Introduction**

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. **Pharmacology**

The effects of chenodeoxycholic acid on the metabolism and secretion of bile acids are well known. Metabolism of bile acids is tightly controlled via a negative feedback regulation of bile acid synthesis. The applicant has provided a review of the pharmacological properties of CDCA. When given orally
CDCA reduces biliary cholesterol secretion, and increases the proportion of biliary CDCA from approximately 33% originally to 70 to 95%, at the expense of formation of cholic acid and deoxycholic acid.

### 2.3.3. Pharmacokinetics

Following ingestion, absorption of CDCA will first be by the small intestine, and is then transported to the liver by the blood for further processing and conjugation with either taurine or glycine. The absorption of CDCA and other bile acids are already clinically well recognised and established, and pharmacokinetic characteristics for distribution, metabolism and excretion have been adequately described from the literature.

### 2.3.4. Toxicology

#### General toxicity:

Single-dose toxicity studies were carried out by oral administration to hamsters, rats, rabbits, dogs and monkeys. Hamsters were the most sensitive species, with females being the more sensitive, followed by rats, rabbits, dogs and primates. Findings considered CDCA-related were diarrhoea, decreased motor activity, flaccidity, atonia, prostration, fasciculation, bradypnea, dyspnoea, salivation.

A number of repeat-dose studies have been reported with CDCA, and with a CDCA form with an olefin group (WP222). These have been completed in rats, hamster, dogs, monkeys (rhesus and squirrel) and baboons. The majority of species have been studied in excess of 6 months, and non-human primates were treated for up to 18 months.

A number of deaths were reported in high and mid-dose groups treated with CDCA, in baboons (120 & 320 mg/kg/day), squirrel monkeys (10-130 mg/kg/day), rhesus monkeys (40-120 mg/kg/day) and dogs (250 & 500 mg/kg/day). The cause of death was in most cases due to treatment with CDCA, and due in some part to liver injury in all species.

The primary toxic effect of CDCA in rats, hamsters, monkeys and baboons is on the hepatobiliary system (liver and bile duct), similar to the toxicity of other bile acids. Findings included increased liver weights, alterations in serum chemistry parameters indicative of hepatic (ALT, AST) and biliary (ALP and bilirubin) toxicity. Diarrhoea, gastrointestinal irritation and/or mucosal congestion were sometimes observed in the primate species at the high doses tested.

#### Genotoxicity:

Conflicting results on potential genotoxicity of CDCA in vitro have been presented by the applicant. However these studies were performed in only two strains of *Salmonella typhimurium*. It has also been seen in other Ames studies that CDCA was not mutagenic. There was also no evidence of mutagenicity in the in vivo rat dominant lethal assay. It is therefore unlikely that CDCA acid can be considered a mutagen.

#### Carcinogenicity:

CDCA has been tested for its carcinogenic potential in a long term toxicity studies in hamsters and in a single GLP 2-year rat bioassays. CDCA was not carcinogenic at doses of up to 120 mg/kg/day and 60 mg/kg/day in hamsters and rats, respectively.
Histological changes in the livers were observed in hamsters which consisted of increased bile duct proliferation and elevations in AST and ALT, although these liver changes are considered consistent with other signs of hepatotoxicity observed in other general toxicity studies.

In addition, the applicant has presented several literature articles in which CDCA was co-administered with known rodent carcinogens to determine whether CDCA could act as a pro-carcinogen. In these studies it was shown that when administered in combination with known carcinogens, CDCA induced a higher level of intestinal tumours, aberrant crypt foci in the colon and hepatocellular foci. It is noted that the relative exposure levels of CDCA (and its conjugates) in these studies are not physiologically relevant and present an extreme situation when used together with other potent known carcinogens.

Overall CDCA is not considered to be carcinogenic in hamsters and rats following long term treatment.

**Reproductive toxicity:**

The reproductive toxicity of CDCA was evaluated in fertility and early embryonic development study in rats, embryo-fetal development studies in rats, hamsters and monkeys, and a pre-postnatal study in rats. None of these studies were completed in compliance with GLP. However, they were completed prior to this requirement implementation. The documentation and summaries were therefore acceptable given the context of this application.

There were no significant adverse treatment-related effects on fertility or early embryonic development, there were no CDCA-related effects on corpora lutea, or number of implantation sites.

For embryofetal development, there was no evidence of teratogenicity or increase in embroyolethality in rats, hamsters or rhesus monkeys. The only significant finding was in non-human primates where there was evidence of changes in the liver (inflammatory cell infiltration and bile duct reduplication, or congestion of veins and sinusoids, and hepatic cell necrosis). Pathological effects on adrenals and kidneys were also seen in rhesus monkey fetuses. The pre and post-natal study completed in rats revealed no changes in terms of behaviour, appearance and bodyweights to offspring. There was evidence of a reduction in pup weight at the mid to high dose groups, but these weight changes fluctuated and were not consistent of the course of the study.

### 2.3.5. Ecotoxicity/environmental risk assessment

Chenodeoxycholic acid is an endogenous bile acid, which will be degraded and/or metabolised in environmental compartments without any Persistence, Bioaccumulation and Toxicity (PBT) risks.

The applicant has provided a Phase I assessment to support the position that CDCA would not pose a risk to the environment when administered as 250 mg capsules. PEC\_surfacewater calculated to be 0.01 µg/L represents a worst case scenario (assuming 100% market penetration).

<table>
<thead>
<tr>
<th>Substance (INN): Chenodeoxycholic acid</th>
<th>PEC_surfacewater, default or refined (e.g. prevalence, literature)</th>
<th>0.01</th>
<th>µg/L</th>
<th>&gt; 0.01 threshold N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other concerns (e.g. chemical)</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
</tr>
</tbody>
</table>
2.3.6. Discussion on non-clinical aspects

No new non-clinical studies have been performed as sufficient non-clinical data was considered available. The applicant relies on the data from the reference medicinal product and literature for all non-clinical aspects. The non-clinical development of CDCA as a medicinal product was performed over 30 years ago and in accordance with regulatory standards of the day. Extensive toxicology studies were conducted in the past and literature data were provided to support the pharmacology, pharmacokinetics and parts of the toxicology programme.

Animal models of CTX disease have not been described. The argument was that the pharmacological action of the endogenous CDCA is already well known and so the lack of strong supportive non-clinical evidence is superseded by the clinical pharmacology. In the context of this application, the concept of using chenodeoxycholic acid in the treatment of inborn errors of bile acid biosynthesis in CTX patients was supported.

In line with the recommendations of ICH S7A, safety pharmacology studies should address the main physiological systems such as the cardiovascular, respiratory and central nervous systems. In this dossier, no safety pharmacology data was provided but reference was made to the presented toxicological studies completed in rats, dogs and non-human primates. No significant changes in safety pharmacology endpoints such as to behaviour, cardiovascular or respiratory have been observed in these studies. The data provided by the applicant was sparse. However, taking into account the clinical experience with CDCA and the case of evaluating safety pharmacology endpoints as a part of the toxicology studies, no concerns were raised from a safety pharmacology standpoint.

No dedicated juvenile toxicity study was conducted. However, the Applicant has argued that a number of studies for chronic general toxicity used young animals, in addition to the completed reproductive toxicity studies. No differences in toxicity profile could be attributed to age of study animals.

The applicant has not provided a full ERA, based upon the argument that CDCA is an endogenous substance and is found extensively in nature. Although compounds such as these are no longer exempted as stated in the recently revised CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2 *), the applicant’s argument has been accepted by the CHMP. Phase I assessment supports the position that CDCA does not pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The submitted non-clinical data support the clinical use of Chenodeoxycholic acid in the treatment of CTX. Cross-references to Xenbilox as well as published data in the scientific literature were considered adequate by the CHMP.
2.4. **Clinical aspects**

2.4.1. **Introduction**

The clinical trial programme comprised two retrospective studies and was supported by literature review. No studies have been performed to determine the pharmacokinetic characteristics of chenodeoxycholic acid. The applicant has provided a literature review of bile acid kinetics and referred to the data available for the reference medicinal product.

**GCP**

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

**Table 2: Overview of clinical studies**

<table>
<thead>
<tr>
<th>Study Code</th>
<th>Study Title</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDCA-STUK-15-001 (Pivotal)</td>
<td>Retrospective Cohort Study to Investigate the Safety and Efficacy of Chenodeoxycholic Acid (CDCA) in Patients Affected by Cerebrotendinous Xanthomatosis (CTX)</td>
<td>Retrospective, single arm, cohort study: Children and Adults</td>
</tr>
<tr>
<td>CDCA-STRCH-GR-14-001</td>
<td>Retrospective Cohort Study to Investigate the Safety and Efficacy of Chenodeoxycholic Acid (CDCA) in Patients Affected by Cerebrotendinous Xanthomatosis (CTX)</td>
<td>Retrospective, single arm, cohort study: Adults</td>
</tr>
</tbody>
</table>

2.4.2. **Pharmacokinetics**

**Absorption**

Orally administered bile acids are absorbed by passive diffusion through plasma membranes along the length of the gastrointestinal tract, because of their hydrophobicity. Glycol- and taurine-conjugated bile acids are absorbed at ileum through receptor-mediated transportation (apical sodium-dependent bile-acid transporter, ASBT). In the presence of enteral bacteria, a portion of chenodeoxycholic acid may be dehydroxylated to form secondary bile acid. Absorbed CDCA enters the blood stream of the portal vein, and is taken up by hepatocyte via Na+-dependent and Na+-independent transporters.

CDCA is completely absorbed when taken fasting or with meals. In man, it appears that unconjugated CDCA is completely absorbed from the small intestine after single doses of up to 400mg. Peak serum concentrations occur 50 to 120 minutes after ingestion. There was no difference in peak concentration but the peak time was later when CDCA was ingested with a meal. (Van-Berge Henegouwen 1977). In a review of the pharmacological properties of CDCA, it was noted that when CDCA is taken with food, its absorption is delayed but bioavailability is not altered (Iser 1981).

**Distribution**

Distribution is mainly limited to the organs involved in the enterohepatic circulation: the intestine, portal circulation, liver and biliary tree, where CDCA exerts its major pharmacological actions. Plasma concentrations reflect the balance between intestinal input and hepatic extraction, and in liver disease the contribution of hepatic efflux due to diminished canalicular secretion will play a significant role. Therefore the therapeutic effectiveness of exogenous bile acids appears to be better related to the degree of biliary enrichment rather than the plasma concentration attained.
**Elimination**

Removal of conjugated bile acids from hepatic cells to biliary canaliculi through receptor-mediated transportation, and bile is stored at gallbladder. Dietary fat stimulates secretion of bile salts. In total about 20 to 30 grams of bile acid are secreted into the intestine daily. About 90% of excreted bile acids are reabsorbed by active transport in the ileum and recycled that is called “enterohepatic circulation”. About 95% of bile acids in the portal circulation are actively up-taken by hepatocyte. The rest 5% enters systemic circulation. In the kidney, bile acids pass glomerular filtration, and are reabsorbed by proximal renal tubular cells. The un-absorbed bile acids are excreted from urine. As a result, about 600 mg of bile salts are synthesized daily to replace bile acids lost in the faeces and urine.

**Metabolism**

In physiologic condition, bile acids conjugate with amino acids, glycine or taurine, to form bile salts. Conjugated bile acids have lower pKa (1 to 4), which makes them much water soluble and easy to emulsify fats at small intestine. In pathologic condition, bile acids conjugate UDP through stimulation of UGT expression. Conjugated bile acids become removable from hepatocytes.

Once absorbed, CDCA is bound to plasma proteins and cleared efficiently by the liver. Subsequent clearance from the plasma is also efficient, so that fasting serum levels of CDCA are barely detectable. In the liver exogenous CDCA is conjugated with glycine more than taurine, and secreted into bile along with the pool of endogenous bile acids in the enterohepatic circulation. Conjugated CDCA is either reabsorbed in the terminal ileum, or deconjugated before either excretion or conversion to LCA. Absorbed LCA is conjugated and sulfated in the liver to reduce reabsorption on recycling. Thus, continued hepatic sulfation and intestinal excretion of LCA prevent accumulation in bile. (Iser, 1981)

**Special populations**

No data is available.

**Pharmacokinetic interaction studies**

Since CDCA is an endogenous bile acid used to replace a deficiency in CDCA in CTX patients, formal pharmacodynamics drug interaction studies have not been undertaken, and are not considered to be necessary.

Data on identified and potential interactions between CDCA and other medicines originate from the use of CDCA in dissolution of gallstones. CDCA is known to bind with colestyramine, colestipol (both bile acid sequestrants) or antacid drugs containing aluminium hydroxide and/or smectite (aluminium oxide) in the intestine, thus preventing its reabsorption and efficacy. Consequently, the above listed medicines should not be administered together with CDCA.

Additionally, oral contraceptives, drugs containing oestrogens and clofibrate may increase the cholesterol concentration of the bile. The administration of oral contraceptives reduces the pool size of chenodeoxycholic acid. This may worsen the underlying deficiency and counteract the effectiveness of chenodeoxycholic acid in CTX. Co-administration with oral contraceptives is not recommended.

**2.4.3. Pharmacodynamics**

No pharmacodynamics studies have been conducted with CA by the applicant.
**Mechanism of action**

In CTX, deficiency of chenodeoxycholic acid causes a lack of feedback of cholesterol 7 alpha hydroxylase (CYP7A1) and HMG CoA reductase, causing increased production of atypical bile acids, bile alcohols and cholestanol that lead to the pathological consequences of the condition. Exogenous replacement with Chenodeoxycholic acid inhibits CYP7A1 (via nuclear receptor, FXR) and HMG CoA reductase, thus restoring the feedback inhibition.

**Primary pharmacology**

The primary pharmacodynamic effects of chenodeoxycholic acid are:

- Reduced production of cholesterol: reduces serum cholestanol (action on HMG CoA reductase).
- Reduced production of cholestanol: reduces serum cholestanol (action on HMG CoA reductase and CYP7A1).
- Reduced production of atypical bile alcohols and bile acids: through restoration of feedback inhibition of primary bile acid synthesis (action on CYP7A1).

Bile acids have a multitude of functions as shown in Table 5 below. The individual contribution of different primary bile acids and their various conjugates have only been partially elucidated.

**Table 3: Physiological Functions of Bile Acids**

**A. In the liver**

1. Generate bile flow through upregulation of bile acid transporters
2. Induce biliary lipid secretion
3. Modulate cholesterol homeostasis through regulation of synthesis and catabolism
4. Regulation of lipoprotein production

**B. In bile**

1. Desaturate bile cholesterol – reduce lithogenic potential
2. Transport cholesterol
3. Buffer Ca 2+ ion

**C. In the intestine**

1. Form micelles (fat digestion)
2. Accelerate lipid transport, including fat-soluble vitamin (A, D, E) absorption
3. Modulate motility
4. Modulate GI hormone output
5. Induce ion (and water) secretion

**Secondary pharmacology**

No secondary pharmacological effects of CDCA have been reported in the literature. CDCA use in CTX is to replace a deficient or absent endogenous substance to physiological levels. CDCA has important
functions as a metabolic regulator and signalling molecule. Thus, no secondary pharmacological effects are expected with CDCA replacement therapy in CTX.

2.4.1. Discussion on clinical pharmacology

Chenodeoxycholic acid has been studied in the literature in terms of its pharmacokinetics and pharmacodynamics, and to a lesser degree as an exogenous pharmacological agent. Although chenodeoxycholic acid is a physiological compound, it cannot be assumed that it will behave the same way when administered as exogenous pharmacological agent. In this regard, a pharmacokinetic study with the proposed medicinal product would have been useful. However, chenodeoxycholic acid has been used for many years as a therapeutic agent. Furthermore, since the pharmacological effects of bile acids are mainly limited to the entero-hepatic circulation rather than plasma, the therapeutic effectiveness of bile acids appears related to the degree of biliary enrichment rather than the plasma concentrations attained. Serial sampling of the bile pool would give the most meaningful pharmacokinetic data. However, the procedure is highly invasive and it would not be ethical to perform it on a serial basis. It is therefore acceptable that pharmacokinetic studies such as these have not been performed.

The relevant interactions for chenodeoxycholic acid are expected to be those that are also relevant for the other bile acids that are used as medicinal products, i.e. cholic acid and ursodeoxycholic acid and therefore data on these other bile acids can be extrapolated to the applied one. The literature data indicate that some medicinal products may interact with chenodeoxycholic acid and appropriate statements have been included in the SmPC.

2.4.2. Conclusions on clinical pharmacology

The CHMP considered that the available clinical pharmacology data were suitable to support the application for a marketing authorisation of chenodeoxycholic acid. The product information adequately reflects relevant pharmacology data.

2.5. Clinical efficacy

2.5.1. Dose response study

No dose-response or comparative efficacy studies were performed by the Applicant and there have been no prospective controlled studies for CDCA in CTX described in the literature.

The clinical use of CDCA in CTX is spanning 40 years. The usual dose (750mg per day in adults and 15mg/kg/day in children) was chosen empirically by clinicians based on the use of CDCA in the management of gallstone dissolution. It is sometimes increased in cases where the cholestanol and/or bile alcohol levels remain high on the initially prescribed dose.

2.5.2. Main studies

CDCA-STUK-15-001; Retrospective Cohort Study to Investigate the Safety and Efficacy of Chenodeoxycholic Acid (CDCA) in Patients Affected by Cerebrotendinous Xanthomatosis (CTX).
**Methods**

This was a retrospective, single arm, cohort study aimed at collecting clinical, laboratory and physiological data generated in a group of patients affected by CTX and treated with CDCA.

For each patient included in the study, demographic data, medical and CTX history, and all other clinical, instrumental, and laboratory data generated from the beginning of CDCA treatment up to 2 years after (with a minimum of 1 year) and at the last clinical visit, were reported.

On-treatment assessments were compared to assessments at baseline. 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 patients. To include as complete a data set as possible in both the studies 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.

**Study Participants**

Patients satisfying the following criteria were eligible for collection of retrospective data reported in their medical chart:

1. Having read the Information for the Patient and obtained a signed Informed Consent Form;
2. Age between 2 and 75 years;
3. Diagnosis of CTX of at least 1 year’s duration;
4. Having received treatment with CDCA;
5. Having at least one cholestanol level and/or urinary bile alcohol level no more than 3 months prior to treatment with CDCA and one cholestanol level and/or urinary bile alcohol level post-treatment within 2 years from the beginning of therapy with CDCA. If not available, qualitative assessment of cholestanol and/or urinary bile alcohols as recorded in the notes could be considered.

No pre-determined exclusion criteria were defined in the study protocol.

**Treatments**

The patients received CDCA orally at 750 mg/day or 15 mg/kg/day.

The mean (± SD) duration of treatment was 10.74 ± 6.66 years (median 9.00 years, range 0.4-26.3 years). The mean (± SD) dose at the screening visit was 661.2 ± 177.4 mg (median 750.0 mg, range 225-1000 mg).

**Objectives**

The objectives of this study were:

- To evaluate retrospectively the activity of CDCA administered orally 750 mg/day or 15mg/kg/day in reducing the serum level of cholestanol and, in selected cases, urinary bile alcohols;
- To evaluate retrospectively the safety and tolerability of CDCA administered orally 750 mg/day or 15mg/kg/day;
- To evaluate the impact of CDCA treatment in halting, slowing or stabilizing clinical disease through the evaluation of several parameters including disability scores, electrophysiological data, imaging data, laboratory parameters, disease signs and symptoms.
Outcomes/endpoints
The study compared for the efficacy evaluation:

1. Biochemical Outcomes on-treatment to baseline
2. Clinical Outcomes on-treatment to baseline
3. Disability Outcomes on-treatment to baseline

The efficacy endpoints of the study were:

- Serum level of cholestanol;
- Urinary bile alcohols assessments;
- Disease signs and symptoms;
- Neurological disability scale (Rankin scale score, EDSS scale score). The Rankin scale measures the level of disability/dependence and ranges from 0 (perfect health without symptoms) to 6 (death). The EDSS also rates disability and ranges from 0 to 10, with 0.5 unit increments that represent higher levels of disability.
- Cognitive performance;
- Electrophysiological parameters (nerve conduction in the arms and in the legs; needle myography in the arms and in the legs).
- Additional laboratory tests, if available;

The safety endpoints of the study were:

- Adverse events;
- Physical examinations;
- Routine laboratory tests, if available: CBC, including RBC, haematocrit, haemoglobin, WBC, differential count, and platelet count; chemistry panel including BUN, creatinine, sodium, potassium, AST, ALT, total bilirubin, glucose, cholesterol, triglycerides, CPK, LDH.

Sample size
No formal sample size was calculated in advance.

Statistical methods
The following populations were considered for data analysis:

1. Screened population, which included all screened patients;
2. Evaluable population, which included all screened patients with
   a) at least one value or qualitative assessment for cholestanol the same day or before CDCA treatment start and at least one value or qualitative assessment for cholestanol after CDCA treatment start, or
   b) at least one qualitative assessment for urinary bile alcohols the same day or before CDCA treatment start and one qualitative assessment for urinary bile alcohols after treatment start; safety population, which included all screened patients who received at least one dose of CDCA
treatment.

Analysis of demographic and disease characteristics was performed in the screened population. Analysis of current patient clinical condition and efficacy endpoints was performed in the evaluable population.

3. Safety population: Included all screened patients who received at least one dose of CDCA treatment.

Analysis of safety endpoints was performed in the safety population. Quantitative variables were summarized by using n (sample size), arithmetic mean, standard deviation (SD), median, minimum and maximum. Categorical variables were summarized by using frequency count and percent distribution.

Results

Conduct of the study
The study was conducted in one study centre in the Netherlands. The mean (± SD) dose of CDCA at the screening visit was 661.2 ± 177.4 mg (median 750.0 mg, range 225-1000 mg).

Numbers analysed
Data was available for 35 patients for the initial screening and baseline visit, for 32 patients (91.4% of enrolled) for post-treatment Visit 1, and for 33 (94.3%) for post-treatment Visit 2 and clinical current condition visit. All 35 screened patients (100.0%) completed the study. The age at first treatment was < 21 years in 15 patients (42.9%) and was ≥ 21 years in 20 (57.1%).

Outcomes and estimation

Biochemical outcomes
The serum levels of cholestanol are summarised in in Table 6 below.
Table 4: Results of serum levels of cholestanol (μmol/l)) during the study period (evaluable population)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-treatment Visit 1</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-73.483 to -39.291</td>
</tr>
<tr>
<td>p value (paired t-test)</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-treatment Visit 2</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>n=25</td>
<td>76.348 ± 40.007</td>
<td>7.728 ± 3.564</td>
<td>-68.620 ± 39.595</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-84.964 to -52.276</td>
</tr>
<tr>
<td>p value (paired t-test)</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Clinical current condition Visit</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=23</td>
<td>72.104 ± 38.413</td>
<td>9.096 ± 6.538</td>
<td>-63.009 ± 39.560</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-80.116 to -45.902</td>
</tr>
<tr>
<td>p value (paired t-test)</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

n = number of observations
Source: Section 14, Table T14.2.1.1

Sub group analysis

<table>
<thead>
<tr>
<th>Age subgroup</th>
<th>Visit 1 Mean change from baseline (95% CI)</th>
<th>Visit2 Mean change from baseline (95% CI)</th>
<th>Current Visit Mean change from baseline (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 21 years</td>
<td>-34.792 (-47.190, -22.393)</td>
<td>-52.754 (-69.821, -35.687)</td>
<td>-48.750 (-69.264, -28.236)</td>
</tr>
<tr>
<td>&gt;=21 years</td>
<td>-79.945 (-108.839, -51.052)</td>
<td>-85.808 (-113.725, -57.891)</td>
<td>-78.564 (-106.956, -50.171)</td>
</tr>
</tbody>
</table>

The levels of Urinary bile alcohols are summarised in in Table 7 below.
Data were missing in more than 25% of the patients. All patients had elevated urinary bile alcohols at baseline. In patients for whom data were available, the majority had improved. A total of 86% (18/21), 100% (19/19) and 79% (11/14) patients improved at Visit 1, Visit 2 and current Visit respectively and the results were statistically significant (p<0.001). In about 10% of the patients, the urinary bile alcohols level remained elevated.

**Subgroup analysis**

<table>
<thead>
<tr>
<th>Age subgroup</th>
<th>Visit 1</th>
<th>Visit 2</th>
<th>Current Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% improved*</td>
<td>Mean change</td>
<td>% improved*</td>
</tr>
<tr>
<td>&lt; 21 years</td>
<td>59% (8/13)</td>
<td>54% (7/13)</td>
<td>38% (5/13)</td>
</tr>
<tr>
<td>&gt; 21 years</td>
<td>56% (9/16)</td>
<td>62% (10/16)</td>
<td>31% (5/16)</td>
</tr>
</tbody>
</table>

Mildly elevated or normal level.

At least a third of patients in both groups had improved. The treatment effect was similar between the two age groups.

**Clinical Outcomes**

*Disease signs and symptoms*

The disease and symptoms at baseline, at post-treatment visits 1 and 2 and at the current clinical condition visit (evaluable population) are shown in Table 8 below.
At baseline, 74% (23/31) presented with diarrhoea which resolved in all patients by the current visit i.e. 100% response. The improvement in cataract was mostly driven by the fact that 64% of the patients had their cataracts removed. There were little or no differences in the proportion of patients with the remaining clinical signs/symptoms compared to baseline.
In the group of patients who presented with clinical symptoms at baseline (Group 1), stabilisation or improvement was seen in at least 19% (6/31) of the evaluable patients at the current visit. In the group of patients with absent clinical symptoms at baseline (Group 2), 11 patients have deteriorated.

**Neurological disability**

**Table 7: Results of Rankin scale (score) during the study (evaluable population)**
In the 26 patients (83.9% of the evaluable cohort) with Rankin Score assessments at both Baseline and Clinical Current Visit, there was an improvement or stabilisation in 22/26 patients (84.6 %,) with Rankin scores improving in 4/26 (15.4 %) and stabilising in 18/26 (69.2%). In 4/26 patients (15.4 %,), Rankin scores deteriorated.

The mean score of the Rankin scale increased slightly (i.e. slightly worsened) from baseline to any post-baseline visit. The increase from baseline was not statistically significant at any post-baseline visit.

In the 26 patients (83.9% of the evaluable cohort) with EDSS scores at both Baseline and Clinical Current Visit, there was an improvement or stabilisation in 20/26 patients (76.9%) with EDSS scores improving in 6/26 (23.1%) and stabilising in 14/26 (53.8%). In 6/26 patients (23.1%), EDSS scores deteriorated over the course of the study. The mean score of the EDSS scale slightly increased (i.e. slightly worsened) from baseline to any post-baseline visit. The increase from baseline was not statistically significant at any post-baseline visit.

The mean (± SD) changes from baseline were 0.12 ± 0.48 (95% CI, -0.08 to 0.32; p = 0.228) at posttreatment Visit 1, 0.25 ± 0.83 (95% CI, -0.12 to 0.62; p = 0.171) at post-treatment Visit 2, and 0.27 ± 1.24 (95% CI, -0.23 to 0.77; p = 0.280) at the clinical current condition Visit.

The median score did not change from baseline to post-treatment Visits 1 and 2, whereas it was 1.25 at baseline and 0.00 at the clinical current condition Visit.

No statistically significant changes from baseline to any post-baseline visit were also observed in the distribution of patients with EDSS ≤ 4 or > 4 (p = 0.317 at both post-treatment Visit 1 and posttreatment Visit 2, p = 0.083 at the clinical current condition Visit.)
Supportive study

CDCA-STRCH-CR-14-001

Retrospective Cohort Study to Investigate the Safety and Efficacy of Chenodeoxycholic Acid (CDCA) in Patients Affected by Cerebrotendinous Xanthomatosis (CTX)

Methods

This was a retrospective, single arm, cohort study collecting clinical, laboratory and physiological data generated in a group of patient affected by CTX, treated with CDCA orally at 750 mg/day, followed in the investigational study site in Italy. The mean (± SD) dose of CDCA at the screening visit was 741.1 ± 47.2 mg (median 750.0 mg, range 500-750 mg). The median follow-up of 5.75 years (range 0-25 years).

For each patient included in the study, demographic data, medical and CTX history, and all other clinical, instrumental, and laboratory data generated from the beginning of CDCA treatment up to 2 years after (with a minimum of 1 year) and the last clinical visit, were reported.

Study participants

Patients satisfying following criteria were eligible for collection of retrospective data reported in their medical chart:

1. Having read the Information for the Patient and obtained a signed Informed Consent Form;
2. Age between 2 and 75 years;
3. Diagnosis of CTX of at least 1 year’s duration;
4. Having received treatment with CDCA;
5. Having at least one cholestanol level no more than 3 months prior to treatment with CDCA and one value post-treatment within 2 years from the beginning of therapy with CDCA;
6. Having at least 1 routine laboratory evaluation no more than 3 months prior to treatment with CDCA and at least 1 post-treatment laboratory evaluation within 2 years from the beginning of therapy with CDCA;

Twenty-eight patients performed both the initial screening visit and the baseline visit, 26 (92.9% of enrolled) performed the post-treatment Visit 1, 21 (75.0%) performed the post-treatment Visit 2, and 26 (92.9%) performed the clinical current condition Visit. Twenty-five patients (89.3%) completed the study and 3 (10.7%) were discontinued.

Objectives and endpoints

The objectives of this study were:

- To evaluate retrospectively the activity of CDCA administered orally 750 mg/day in reducing the serum level of cholestanol and, in selected cases, other bile acid precursors;
- To evaluate retrospectively the safety and tolerability of CDCA administered orally 750 mg/day;
- To evaluate the impact of CDCA treatment in halting, slowing or stabilizing clinical disease through the evaluation of several parameters including disability scores, electrophysiological data, imaging data, laboratory parameters and bone mineral density.
Outcomes/endpoints

The endpoints of the study were:

- Serum level of cholestanol;
- Neurological disability scale (Rankin scale score, EDSS scale score);
- Cognitive performance (MMSE scale total score, MMSE scale corrected score);
- Bone mineral density (lumbar, total hip, lumbar Z score, total hip Z score, lumbar vBMD, femoral neck vBMD);
- Electrophysiological parameters:
  - For right/left superior/inferior limbs: latency at rest, motor evoked potential (LrMEP), Central Motor Conduction Time (CMCT), Interside Difference (ISD);
  - For deep peroneal/tibial/sural/superficial peroneal/ulnar nerves: Motor Conduction Velocity (MCV), Compound Muscle Action Potential amplitude (CMAPa);
  - For sural/superficial peroneal/ulnar nerves: Sensory Conduction Velocity (SCV), Sensory Potential amplitude (SAPa);
  - H-reflex right/left inferior limbs;
- Additional laboratory tests (CPK, LDH, lactate, pyruvate, 7a-hydroxy-4-cholesten-3-one, 27-hydroxycholesterol, Vitamin D, PTH, serum and urinary phosphate and calcium);
- Adverse events;
- Physical examinations;
- Routine laboratory tests: complete blood count (CBC), including RBCs, hematocrit, hemoglobin, WBCs, differential count, and platelet count; chemistry panel including BUN, creatinine, sodium, potassium, AST, ALT, total bilirubin, glucose, cholesterol, triglycerides.

Statistical methods

The methods were the same as previously described for study CDCA-STUK-15-001.

Outcomes and estimation

Biochemical outcomes

The serum levels of cholestanol are summarised in in Table 12 below.

Table 9: Results of serum cholestanol during the study period
A total of 26/28 screened patients were included in the evaluable population. Twenty-five patients (89.3%) completed the study and 3 (10.7%) were discontinued.

The results indicate a significant reduction in serum cholestanol level compared to baseline ($p < 0.001$). The decrease from baseline ranged from 2.62 to 2.84 mg/dl.

**Clinical Outcomes**

*Disease signs and symptoms*

The disease and symptoms at baseline, at post-treatment visits 1 and 2 and at the current clinical condition visit (evaluable population) are shown in Table 13 below.

**Table 10: Disease and symptoms at baseline, at post-treatment visits 1 and 2 and at the current clinical condition visit (evaluable population)- n(%)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-treatment Visit 1</th>
<th>Post-treatment Visit 2</th>
<th>Current clinical condition Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhoea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>12/46(15)</td>
<td>15/57.7%</td>
<td>14/53.8%</td>
<td>15/57.7%</td>
</tr>
<tr>
<td>Present</td>
<td>14/53.9%</td>
<td>11/41.3%</td>
<td>7/28.9%</td>
<td>11/42.3%</td>
</tr>
<tr>
<td>Worsened</td>
<td>1/0.1%</td>
<td>0/0.0%</td>
<td>1/0.1%</td>
<td>1/0.1%</td>
</tr>
<tr>
<td>Stable</td>
<td>5/18.5%</td>
<td>6/21.9%</td>
<td>9/31.8%</td>
<td>9/31.8%</td>
</tr>
<tr>
<td>Improved</td>
<td>5/18.5%</td>
<td>3/11.1%</td>
<td>1/0.1%</td>
<td>1/0.1%</td>
</tr>
<tr>
<td><strong>Xanthomas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>5/19.2%</td>
<td>5/19.2%</td>
<td>1/11.1%</td>
<td>5/19.2%</td>
</tr>
<tr>
<td>Present</td>
<td>21/80.8%</td>
<td>21/80.8%</td>
<td>18/68.9%</td>
<td>21/80.8%</td>
</tr>
<tr>
<td>Worsened</td>
<td>3/14.3%</td>
<td>1/11.1%</td>
<td>6/23.1%</td>
<td>6/23.1%</td>
</tr>
<tr>
<td>Stable</td>
<td>18/68.9%</td>
<td>17/64.4%</td>
<td>4/15.4%</td>
<td>15/57.7%</td>
</tr>
<tr>
<td><strong>Cataract</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>3/11.5%</td>
<td>3/11.5%</td>
<td>1/11.5%</td>
<td>3/11.5%</td>
</tr>
<tr>
<td>Present</td>
<td>23/88.5%</td>
<td>22/88.5%</td>
<td>20/78.6%</td>
<td>23/88.5%</td>
</tr>
<tr>
<td>Worsened</td>
<td>2/8.5%</td>
<td>0/0.0%</td>
<td>1/6.2%</td>
<td>1/6.2%</td>
</tr>
<tr>
<td>Stable</td>
<td>18/68.9%</td>
<td>17/64.4%</td>
<td>1/6.2%</td>
<td>1/6.2%</td>
</tr>
<tr>
<td>Improved</td>
<td>1/4.4%</td>
<td>1/4.4%</td>
<td>0/0.0%</td>
<td>0/0.0%</td>
</tr>
<tr>
<td><strong>Cognitive impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>6/23.1%</td>
<td>5/19.2%</td>
<td>1/11.1%</td>
<td>4/15.4%</td>
</tr>
<tr>
<td>Present</td>
<td>20/76.9%</td>
<td>19/76.9%</td>
<td>16/63.6%</td>
<td>22/84.4%</td>
</tr>
<tr>
<td>Worsened</td>
<td>2/8.5%</td>
<td>0/0.0%</td>
<td>0/0.0%</td>
<td>1/6.2%</td>
</tr>
<tr>
<td>Stable</td>
<td>18/68.9%</td>
<td>17/64.4%</td>
<td>16/64.4%</td>
<td>16/64.4%</td>
</tr>
<tr>
<td>Improved</td>
<td>1/4.4%</td>
<td>0/0.0%</td>
<td>0/0.0%</td>
<td>0/0.0%</td>
</tr>
<tr>
<td><strong>Psychiatric impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>13/50.0%</td>
<td>12/46.4%</td>
<td>10/58.8%</td>
<td>12/50.0%</td>
</tr>
<tr>
<td>Present</td>
<td>13/50.0%</td>
<td>13/50.0%</td>
<td>11/44.6%</td>
<td>13/50.0%</td>
</tr>
<tr>
<td>Worsened</td>
<td>2/6.9%</td>
<td>0/0.0%</td>
<td>1/11.1%</td>
<td>1/11.1%</td>
</tr>
<tr>
<td>Stable</td>
<td>9/32.1%</td>
<td>10/38.1%</td>
<td>12/46.4%</td>
<td>12/46.4%</td>
</tr>
<tr>
<td>Improved</td>
<td>2/14.3%</td>
<td>1/3.6%</td>
<td>0/0.0%</td>
<td>0/0.0%</td>
</tr>
<tr>
<td><strong>Necrointestinal impairment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>6/23.1%</td>
<td>6/23.1%</td>
<td>4/23.1%</td>
<td>6/23.1%</td>
</tr>
<tr>
<td>Present</td>
<td>20/76.9%</td>
<td>20/76.9%</td>
<td>16/61.5%</td>
<td>20/76.9%</td>
</tr>
<tr>
<td>Worsened</td>
<td>1/8.5%</td>
<td>1/8.5%</td>
<td>0/0.0%</td>
<td>1/8.5%</td>
</tr>
<tr>
<td>Stable</td>
<td>16/61.5%</td>
<td>12/80.0%</td>
<td>9/45.0%</td>
<td>9/45.0%</td>
</tr>
<tr>
<td>Improved</td>
<td>2/14.3%</td>
<td>1/3.6%</td>
<td>0/0.0%</td>
<td>0/0.0%</td>
</tr>
<tr>
<td><strong>Source: Section 14, Table 13.1.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The proportions of patients with or without disease signs and symptoms at current visits are comparable to those at baseline. Unlike in the pivotal study, diarrhoea has not fully resolved as 42% (11/26) of the patients still had diarrhoea at the current visit.
### Neurological disability scales

**Table 11: Results of Rankin scale (score) during the study (evaluable population)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-treatment Visit 1</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=26 (SD)</td>
<td>2.0 ± 1.2</td>
<td>2.3 ± 1.3</td>
<td>0.3 ± 0.5</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>0.1 to 0.5</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>2.0 (0-4)</td>
<td>2.0 (0-4)</td>
<td>0.0 (0-2)</td>
</tr>
<tr>
<td>p value (paired t-test)</td>
<td></td>
<td>0.016</td>
<td></td>
</tr>
</tbody>
</table>

**Table 12: Results of EDSS scale (score) during the study (evaluable population)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-treatment Visit 1</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=26 (SD)</td>
<td>3.50 ± 1.53</td>
<td>3.90 ± 1.96</td>
<td>0.40 ± 0.74</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>0.11 to 0.70</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.5 (0-7.0)</td>
<td>3.75 (0.0-9.0)</td>
<td>0.0 (0.0-2.5)</td>
</tr>
<tr>
<td>p value (paired t-test)</td>
<td></td>
<td>0.010</td>
<td></td>
</tr>
</tbody>
</table>

**Table 11: Results of Rankin scale (score) during the study (evaluable population)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Post-treatment Visit 2</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=21 (SD)</td>
<td>3.19 ± 1.40</td>
<td>3.50 ± 1.69</td>
<td>0.31 ± 0.66</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>0.01 to 0.61</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.0 (0-6.0)</td>
<td>3.5 (0-8.0)</td>
<td>0.0 (-0.5-2.0)</td>
</tr>
<tr>
<td>p value (paired t-test)</td>
<td></td>
<td>0.044</td>
<td></td>
</tr>
</tbody>
</table>

**Table 12: Results of EDSS scale (score) during the study (evaluable population)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Clinical current condition Visit</th>
<th>Change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=26 (SD)</td>
<td>3.50 ± 1.53</td>
<td>4.40 ± 2.20</td>
<td>0.90 ± 1.13</td>
</tr>
<tr>
<td>95% CI</td>
<td></td>
<td>0.45 to 1.36</td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.5 (0-7.0)</td>
<td>4.0 (0-8.0)</td>
<td>0.5 (-0.5-4.0)</td>
</tr>
<tr>
<td>p value (paired t-test)</td>
<td></td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

n = number of observations

Source: Section 14, Table T14.2.2
Rankin scale

There was no deterioration in Rankin score in 61.5% of patients over the course of the study (range of follow-up in these patients was 0.5-13.6 years). The mean score of the Rankin scale increased (i.e. worsened) from baseline to any post-baseline visit. The mean (± SD) changes from baseline were 0.3 ± 0.5 (95% CI, 0.1 to 0.5; p = 0.016) at post-treatment Visit 1, 0.1 ± 0.4 (95% CI, -0.0 to 0.3; p = 0.083) at post-treatment Visit 2, and 0.5 ± 0.6 (95% CI, 0.2 to 0.7; p = 0.001) at the clinical current condition Visit. The median change from baseline were 0.0 at any post-baseline visit.

EDSS scale

There was no deterioration in EDSS scores in 50% of patients over the course of the study (range of follow-up in these patients was 0.5-13.6 years). The mean score of the EDSS scale significantly increased (i.e. worsened) from baseline to any post-baseline visit. The mean (± SD) changes from baseline were 0.40 ± 0.74 (95% CI, 0.11 to 0.70; p = 0.010) at post-treatment Visit 1, 0.31 ± 0.66 (95% CI, 0.01 to 0.61; p = 0.044) at post-treatment Visit 2, and 0.90 ± 1.13 (95% CI, 0.45 to 1.36; p<0.001) at the clinical current condition Visit. The median changes from baseline were 0.0 at post-treatment Visits 1 and 2, and 0.50 at the clinical current condition Visit.

Literature review

The Applicant has undertaken a systematic review of published literature on the use of oral CDCA in the treatment of CTX and complied with the standard reporting guidelines for systematic review (PRISMA). The search 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. A total of 112 articles were reviewed, and 70 articles were selected. Of these, 39 case series (2 or more patients) and 31 case reports (single cases). The Applicant also presented narratives of selected case series. There were no randomised, controlled trials in CTX.

Literature on treatment of CTX patients is dominated by oral CDCA supplementation. Since 1975, at least 70 studies have been published involving approximately 200 patients. In some cases other treatments where added to CDCA treatment or separately tested such as UDCA, simvastatin, pravastatin and LDL-apheresis. The age of the CTX patients at the start of treatment varied between 2 months and 64 years, and patients were followed for a period ranging from 1 month up to 18 years. The common adult dosage studied was 750 mg per day or 15 mg/kg three times daily, however lower doses such as 300 mg/day were also studied. Response was measured in various ways including the biochemical parameters, serum cholesterol and cholestanol, bile acids and their metabolites in plasma, and bile, urine and cerebrospinal fluid (CSF) concentrations of cholestanol. Clinical parameters included cessation of diarrhoea, prevention or halt of cataract, improvement in neuropsychological and peripheral neurologic symptoms, bone density and prevention of progressive neurological dysfunction.

A total of 204 patients’ data was included in the overall efficacy summary based on published literature. Biochemical data was available in 174 (156+18) cases and a response was seen in all 174 patients. (174/174, 100%). Biochemical response was given numerically in many cases but given the variability in units, combining data for comparison was not feasible and therefore the author’s conclusion was only included (significant reduction, normalisation- of cholestenol/bile alcohols).

Neurological impairment was reported in a total of 97 patients, with stabilisation (or improvement) seen in 71 patients (71/97, 73.2%) and deterioration in 26 patients (26/97, 26.8%).

Cognitive impairment was reported in 35 patients, with 31 patients stabilising (or improving) on treatment (31/35, 88.6%). Continued deterioration in cognitive impairment was reported in 4 patients,
on treatment. (4/35, 11.4%). The rate of deterioration was not described. Diarrhoea was reported in only 17 patients and was reported as resolved in 16 (16/17, 94.1%) with treatment.

Epilepsy was reported in 18 patients, 16 patients showed an improvement with CDCA (16/18, 88.9%) and 2 (2/18, 11.1%) did not. Improvement or stabilisation in Xanthomas was reported in 2 patients.

Overall, there was a universal biochemical response in CTX patients with CDCA. In terms of clinical response, over 70% of patients were reported as showing a stabilisation or improvement in their clinical status.

### 2.5.1. Discussion on clinical efficacy

**Design and conduct of clinical studies**

Although the applicant did not fully explain the choice of dosing regimen, the submitted rationale provides a reasonable scientific justification regarding the recommended dose.

There are no specific validated neurological or disability scales that are available for CTX. The EDSS scale was originally developed for use in multiple sclerosis patients and quantifies disability in eight Functional Systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral and other). A score of 1.0-4.5 refers indicates that patients are fully ambulatory. Cut-off point of 4 was chosen to represent moderate to significant disability due to disease progression. The proportion of patients that progressed over long term follow-up to EDSS scores >=4 representing moderate walking difficulties and increasing need for assistance, is a measure of response to treatment, as with CTX, patients progressively manifest with significant disability through the course of the disease. As the presentation in CTX resembles the presentation of progressive neurodegenerative MS, the EDSS is particularly useful to assess neurological disability and disability in CTX.

The Applicant has presented data on natural progression from pooled Expanded Disability Status Scale (EDSS) and age data in untreated CTX, based on the baseline values from the two retrospective studies and published case series because the majority of the articles on disease progression were published prior to the use of Disability Scales. This approach has been found acceptable. The Rankin score was developed to measure the degree of disability in daily lives of people with stroke or other causes of neurological disability, which is relevant to CTX.

The Applicant defined all the variables and the set of rules for deriving new variables in the statistical analysis plan. This approach is supported. The CHMP noted that all measures of efficacy had a considerable amount of missing data. The Applicant has presented some estimates of treatment effect based on within patients' comparisons. This approach may produce bias results if data are not missing at random and may reduce the precision of the analysis substantially as it is based on complete cases. Therefore, significant results need to be interpreted with caution.

**Efficacy data and additional analyses**

The biochemical efficacy of chenodeoxycholic acid (CDCA) treatment in patients with as cerebrotendinous xanthomatosis (CTX) using widely accepted surrogate marker such as cholestanol and apoprotein B appears to have been shown in the published reports.

The fact that there is no placebo arm, the lack of a control group with active treatment and the known limitations/deficiencies of retrospective studies makes the data difficult to interpret and conclude without uncertainties on the efficacy of the CDCA in CTX. The low prevalence of the disease has also been taken into consideration in the assessment.
The clinical efficacy of CDCA treatment is more difficult to assess than the biochemical efficacy. A formal comparison of the long term clinical outcome of patients suffering from CTX with and without CDCA treatment would have been desirable. However, due to the rarity of the disease and the fact that most of the cases presented were detected at a symptomatic stage of differing severity, a formal study would require the inclusion of many centers and a long observational period to obtain any meaningful results, which would not be feasible in light of the rarity of the disease. Furthermore, since CDCA treatment was shown to improve both the biochemical and clinical symptoms of this serious debilitating disease in many cases, it would not be ethically acceptable to withdraw this therapeutic effect from patients for a longer time period.

It is therefore considered that the data showing biochemical efficacy and the associated improvements regarding the various disease symptoms after CDCA therapy compared with historical data of untreated patients provide sufficient evidence of CDCA’s effectiveness. However, it is likely that due to the multiple nature of therapy (dietary, pharmaceutical, supportive) in these patients, there may be an element of overestimation in the clinical effects of CDCA treatment.

The CHMP noted that apart from the low prevalence of CTX, the seemingly late detection in symptoms lead to irreversible damage, especially to the nervous system and connective tissue, which cannot be corrected by further therapy. Nevertheless, for neurological symptoms after introduction of CDCA therapy, a demonstrable decrease of morbidity was found.

The available clinical data do not allow correlating dosage and clinical efficacy. There is also no evidence of development of tolerance as there were no reported rises in blood levels of cholestanol and apoprotein B during long-term chenodeoxycholic acid treatment.

The formulation administered during the pivotal clinical study (CDCA-STUK-15-001) was the marketed formulation of Xenbilox. For the supportive clinical study (CDCA-STRCH-CR-14-001) a compounded formulation of CDCA 250 mg capsules was manufactured by the hospital pharmacy and the patients were treated with this CDCA compounded locally at the centre’s pharmacy. Results of studies of dissolution comparing the two products demonstrated that, despite minor differences in excipients contained in the compounded and reference formulations, both products can be considered similar. Accordingly, the results of the 2 studies can be considered comparable to support the applied medicinal product.

MA under exceptional circumstances

The CHMP was of the opinion that comprehensive data is unlikely to be generated under normal conditions of use for the following reasons:

*Inability to provide comprehensive efficacy and safety data due to rarity of the indication*

The applied indication is rarely encountered. Indeed, chenodeoxycholic acid has been designated as Orphan Medicinal Product (EU/3/14/1406) by the European Commission for the treatment of inborn errors of primary bile acid synthesis on 16th of December 2014. At the time of designation, inborn errors in primary bile acid synthesis affected not more than 0.2 in 10,000 people in the EU. Given the rarity of the diseases, the CHMP considered that the applicant cannot be reasonably expected to provide comprehensive clinical evidence.

*Inability to collect comprehensive information because it would be contrary to medical ethics*
It would be contrary to medical ethics principles to collect evidence of clinical efficacy of chenodeoxycholic acid in the applied indication in a placebo-controlled clinical study as it would expose patients to severe risks.

In the context of a MA under exceptional circumstances, specific obligation(s) is included in the terms of the Marketing Authorisation. The applicant proposed to monitor the long term efficacy in patients treated with CDCA from a patient registry for which details are reflected in the risk management plan; the CHMP agreed on this proposal. The registry will monitor accumulating data on efficacy in the treatment of CTX in infants, children, adolescents and adults.

2.5.2. Conclusions on the clinical efficacy

The CHMP was of the view that data presented in this application shows both biochemical and clinical benefits of chenodeoxycholic acid therapy in patients with cerebrotendinous xanthomatosis.

The CHMP considers the following specific obligation necessary in the context of a MA under exceptional circumstances:

The Applicant will establish a registry to monitor the long term efficacy in patients treated with CDCA.

2.5.3. Clinical safety

Patient exposure

Clinical data related to the requested indication was obtained mainly from two retrospective non-interventional clinical studies. Long term CDCA use in CTX as described in the scientific literature did not reveal any safety concerns. Additional data was derived from patients with gallstones for whom the reference product was originally authorised. The total exposure for CDCA was estimated to be 5,995 patient treatment years.

In two retrospective studies 63 patients were prescribed CDCA 750 mg/day or 15 mg/kg/day with treatment duration up to 25 years. In the pivotal study, the mean (± SD) duration of CDCA treatment was 10.74 ± 6.66 years (median 9.00 years, range 0.4-26.3 years). The mean (± SD) dose of CDCA at the screening visit was 661.2 ± 177.4 mg (median 750.0 mg, range 225-1000 mg). 11 children were treated at a dose of 15 mg/kg/day.

In the supporting study, the mean (± SD) duration of CDCA treatment was 6.68 ± 5.26 years (median 5.75 years, range 0-25 years) and the mean (± SD) dose of CDCA at the screening visit was 741.1 ± 47.2 mg (median 750.0 mg, range 500-750 mg).

Adverse events

Overall, the study medication appears to have been well tolerated in both retrospective studies. Adverse events from the two retrospective studies are summarised in Table 16 below.
Table 13: Summary of Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>CDCA-STUK-15-001</th>
<th>CDCA-STRCH-CR-14-001</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=35)</td>
<td>(N=28)</td>
</tr>
<tr>
<td>Overall AEs</td>
<td>25 (74.3%)</td>
<td>9 (32.1%)</td>
</tr>
<tr>
<td></td>
<td>76</td>
<td>15</td>
</tr>
<tr>
<td>SAEs</td>
<td>7 (20.0%)</td>
<td>9 (32.1%)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Treatment-related AEs</td>
<td>3 (8.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Mild AEs</td>
<td>23 (55.7%)</td>
<td>1 (3.6%)</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>1</td>
</tr>
<tr>
<td>Moderate AEs</td>
<td>15 (42.9%)</td>
<td>5 (17.9%)</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>6</td>
</tr>
<tr>
<td>Severe AEs</td>
<td>1 (2.9%)</td>
<td>5 (17.9%)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

N = number of patients in the safety population; n = number of patients with events

**CDCA-STUK-15-001**

A total of 76 AEs were reported in 26 patients (74.3%). The most commonly involved SOCs were: surgical and medical procedures (18 AEs in 11 patients, 31.4%), musculoskeletal and connective tissue disorders (7 AEs in 6 patients, 17.1%), general disorders and administration site conditions (5 AEs in 5 patients, 14.3%), and injury, poisoning and procedural complications (5 AEs in 5 patients, 14.3%).

The most common AEs were: cataract operation (6 AEs in 5 patients, 14.3%) and fatigue (4 AEs in 4 patients, 11.4%).

Fifty-three AE of mild intensity were reported in 23 patients (65.7%), 22 AEs of moderate intensity were reported in 15 patients (42.9%), and 1 AE of severe intensity was reported in 1 patient (2.9%).

The AE of severe intensity consisted of fatigue and was not related to the study drug.

The three treatment-related AEs were constipation (2 AEs in 2 patients, 5.7%) and hepatitis toxic (1 AE in 1 patient, 2.9%). None of the treatment-related AEs was serious.

**Study CDCA-STRCH-CR-14-001**

A total of 16 AEs were reported in 9 patients (32.1%). None of the AEs was related with study medication.

There were no treatment-related AEs in any patient during the study. AEs and SAEs were reported in 9 patients (32.1%). AEs of mild intensity were reported in 1 patient (3.6%), and AEs of moderate or severe intensity were both reported in 5 patients (17.9%).

The most commonly involved system organ class (SOCs) were surgical and medical procedures (9 AEs in 6 patients, 21.4%) and gastrointestinal disorders (2 AEs in 2 patients).

**Comparison with reference product safety profile**

Diarrhoea was commonly seen in patients who were prescribed CDCA for gallstone dissolution but not seen in CTX patients. In contrast, diarrhoea is a common disease manifestation of CTX which appears to resolve on treatment with CDCA. Mild, intermittent constipation was seen in 2 CTX patients on treatment with CTX.
PSURs from post marketing experience have not revealed any safety concerns.

**Serious adverse event/deaths/other significant events**

**Study CDCA-STUK-15-001**

A total of 9 SAEs were reported in 7 patients (20.0%).

The SAEs were as follows: gastrostomy, rheumatoid arthritis and urinary incontinence, depression and humerus fracture, angina pectoris, foot operation, pneumothorax, and cataract operation. None of the SAEs were related to the study drug.

**Study CDCA-STRCH-CR-14-001**

There was one fatal event (colon cancer) which was not related to study medication.

A total of 15 SAEs were reported in 9 patients (32.1%).

There were no deaths or treatment-related SAEs reported in any patients following treatment with CDCA.

**Laboratory findings**

**Haematology:**

In the majority of patients who performed the test at both the baseline and the post-treatment Visits 1 and 2, the values of RBCs, haemoglobin, haematocrit, platelet count, WBCs count and differential count were normal at both baseline and post-treatment Visits 1 and 2. Fewer patients showed shifts from normal values at baseline to abnormal NCS values at post-treatment Visits 1 and 2, or abnormal NCS values at baseline that were normalised at post-treatment Visits 1 and 2.

**Clinical biochemistry:**

In the majority of patients who performed the test at both the baseline and the post-treatment Visits 1 and 2, the values of BUN, creatinine, ALT, AST, glucose, sodium, potassium, cholesterol and triglycerides were normal at both baseline and post-treatment Visits 1 and 2. Fewer patients showed shifts from normal values at baseline to abnormal NCS values at post-treatment Visits 1 and 2, or abnormal NCS values at baseline that were normalised at post-treatment Visits 1 and 2.

**Safety in special populations**

No data is available.

**Safety related to drug-drug interactions and other interactions**

Due to limited data and lack of systematic studies, no definite conclusions can be drawn regarding drug-drug or other interactions.

**Discontinuation due to adverse events**

In the absence of any controlled study data, no conclusions can be drawn on discontinuation due to AEs.
**Literature review**

Only 1 relevant article describing an adverse event with CDCA therapy was identified. This single case of suspected toxic hepatitis (Huidekoper, 2015) has already been recorded in the retrospective study and has been described above.

Mild liver abnormalities have been reported in the literature for patients treated with CDCA for gallstones, but it is not clear if they are due to pre-existing disease or treatment.

### 2.5.4. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

There are significant differences in the pathophysiology between CTX and gallstone dissolution, the indication in which Xenbilox has been authorised. These differences impact the extrapolation of safety information at the recommended dose. Therefore, the primary data for safety evaluation has been derived from the retrospective studies in CTX.

In the retrospective studies, CDCA exhibited a satisfactory safety profile, with only 3 treatment-related AEs. Although cases of diarrhoea have also been reported, this is a common symptom of CTX which resolved on therapy.

The uncontrolled nature of the data rendered it difficult to evaluate the causal association. However, it is possible to conclude that the AEs reported with CDCA therapy appeared generally to be not serious and mostly related to the underlying disease condition.

There were no significant changes in either haematological or clinical chemistry parameters during treatment with study medication. Treatment with exogenous primary bile acids is known to cause mild to moderate elevation of liver enzymes. The occurrence of one case of non-serious hepatitis would therefore be consistent with the study medication as a cause and an appropriate statement has been included in the SmPC.

There are no reports on the use of CDCA in patients with renal impairment in the two retrospective studies and none were found in the literature. Under normal physiological conditions, CDCA is primarily excreted in faeces. Excretion through the kidney is negligible, but may increase in cholestasis (Alnouti 2009). FXR activation by CDCA has been shown to modulate renal lipid metabolism, decrease proteinuria and improve renal fibrosis and inflammation in renal damage induced by a high fructose diet in Wistar mice (Hu 2015). As there is no data in renal failure with CDCA administration in patients with CTX, it is advisable that patients with renal impairment are monitored closely during treatment with CDCA. Similarly, as no data is available in patients with liver impairment not related to inborn errors of primary bile acid synthesis, patients with hepatic impairment treated with CDCA should be monitored closely.

**MA under exceptional circumstances**

The CHMP was of the opinion that the applicant was unable to provide comprehensive data on safety under normal conditions of use because the indication for which CDCA is intended is encountered too rarely and further data will have to be collected post-approval.

In the context of a MA under exceptional circumstances a specific obligation is included in the terms of the Marketing Authorisation. The applicant will monitor the long term safety in patients treated with CTX from a patient registry for which details are included in the risk management plan. The registry
2.5.5. Conclusions on clinical safety

The CHMP was of the opinion that the available safety data supports the Application for CDCA in the treatment of cerebrotendinous xanthomatosis.

The CHMP considers the following specific obligation necessary in the context of a MA under exceptional circumstances:

The applicant will monitor the long term safety of CDCA in the treatment of CTX by establishing a patient registry.

2.6. Pharmacovigilance

Risk Management Plan

Safety concerns

A detailed summary of the completed toxicological studies with CDCA are provided in the tables in the RMP separated in sections such as general toxicity, genotoxicity, carcinogenicity and reproductive toxicity. The highlighted safety concerns are supported based on the non-clinical data presented for CDCA and the potential risks for hepatotoxicity given the adverse finding in non-clinical species.

Table 14: Summary of the Safety Concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Hepatic adverse reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important potential risks</td>
<td>Reduction of efficacy caused by concomitant use with: bile acid sequestrants (e.g. colestyramine, colestipol), aluminium hydroxide and/or smectite (aluminium oxide)</td>
</tr>
<tr>
<td>Missing information</td>
<td>Interaction with oral contraceptive Carcinogenicity Teratogenicity Use in pregnant or lactating women Long term data in large patient population</td>
</tr>
</tbody>
</table>

Pharmacovigilance plan

Table 18: Table of Ongoing / Planned Pharmacovigilance activities / Actions in the PV plan
### Study / activity type and category

<table>
<thead>
<tr>
<th>Category 2</th>
</tr>
</thead>
</table>

### Study / activity type and category

<table>
<thead>
<tr>
<th>Study / activity type and category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chenodeoxycholic acid (CDCA) 250 mg post-authorisation patient registry</td>
</tr>
</tbody>
</table>

### Objectives

The objective of this registry will be to collect observational long-term safety and clinical effectiveness data on patients with cerebrotendinous xanthomatosis (CTX) treated with CDCA as per routine clinical care at the respective centres. This will be done by collecting clinically relevant data, as available, including demographic, baseline clinical features, adverse events, laboratory parameters, imaging, disability scores, clinical and biochemical responses and CDCA treatments and follow up.

### Safety concern addressed

Long term safety data in large patient population

### Status

Planned

### Date of submission of the final study report

Study results – 1st submission 2022 (and then 5 yearly)

---

### Risk minimisation measures

#### Table 19: Summary table of the risk minimisation measures

<table>
<thead>
<tr>
<th>Safety concerns</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic adverse reactions</td>
<td>Wording in SmPC section 4.2, 4.4, 4.8, 5.3 Prescription only medicine</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Important potential risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduction of efficacy caused by concomitant use with: bile acid sequestrants (e.g. colestyramine, colestipol), aluminium hydroxide and/or smectite (aluminium oxide)</td>
<td>Wording in SmPC section 4.5 Prescription only medicine</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Missing information</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction with oral contraceptives</td>
<td>Wording in SmPC section 4.4, 4.5 Prescription only medicine</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Carcinogenicity</td>
<td>Wording in SmPC section 5.3 Prescription only medicine</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Teratogenicity</td>
<td>Wording in SmPC section 4.6, 5.3 Prescription only medicine</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Use in pregnant or lactating women</td>
<td>Wording in SmPC section 4.6 Prescription only medicine</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Safety concerns</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-----------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Long term data in large patient population</td>
<td>Prescription only medicine</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>

**Conclusion**

The CHMP and PRAC considered that the risk management plan version 6.0 (dated 09 September 2016) is acceptable.

**Pharmacovigilance**

**Pharmacovigilance system**

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

**PSUR submission**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

**2.7. Product information**

**2.7.1. User consultation**

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

**2.7.2. Additional monitoring**

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Chenodeoxycholic acid sigma-tau is included in the additional monitoring list as it is approved under exceptional circumstances [REG Art 14(8), DIR Art (22)].

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.
3. Benefit-risk balance

Benefits

Beneficial effects

Chenodeoxycholic acid has been shown to have a beneficial effect in patients with CTX. Its clinical use has been documented in the literature since at least the mid-1980s.

In the pivotal study CDCA-STUK-15-001 treatment of CTX patients with chenodeoxycholic acid was associated with statistically significant decreases in mean serum levels of cholestanol and urinary bile level alcohol levels. Neurological disability scale scores (Rankin and EDSS) stabilised or improved by the clinical current visit in 84.6% and 76.9% of patients respectively. Mean Rankin and EDSS scores showed a very small increase (worsening) from baseline to clinical current visit at 0.08 ± 0.74 and 0.27 ± 1.24 in the overall population and this increase was not statistically significant. There was a statistically significant ($p = 0.04$) improvement (decrease) of -0.31 ± 0.48 in the mean Rankin score for the < 21 years of age subgroup.

Disease signs and symptoms resolved, improved or stabilised in a majority of patients over the course of the study. Diarrhoea disappeared in 100% (23/23 patients) of the patients who had this symptom at baseline. There was a resolution, improvement or stabilisation in 88.9% (16/18) of patients with cognitive impairment. Epilepsy resolved in 100% (3/3 patients) and polyneuropathy stabilised or improved in 100% (11/11). Pyramidal dysfunction improved or stabilised in 60% (9/15) and cerebellar dysfunction in 85.7% (12/14). Psychiatric impairment resolved, improved or stabilised in 85.7% (6/7) of patients.

In the supportive study CDCA-STRCH-CR-14-001 treatment of CTX patients with chenodeoxycholic acid was associated with statistically significant decreases in mean serum levels of cholestanol from baseline to any post-baseline visit. The mean levels of 7α-hydroxy-4-cholesten-3-one significantly decreased from baseline to post-baseline Visits 1 and 2. Rankin and EDSS scores remained stable in 61.5% and 50% of patients respectively, however there was an overall worsening of the mean score from baseline. Signs and symptoms of the disease remained stable in most of the patients. Diarrhoea improved or disappeared in 64.3% of the patients who had this symptom present at baseline.

Uncertainty in the knowledge about the beneficial effects.

Clinical experience has been reported in the literature from small cohorts of patients and single case reports; absolute patient numbers are small due to the rarity of the condition. This rarity also made the conduct of controlled clinical studies unfeasible. Many of the patients in published reports were treated with bile acids preparations in which CDCA was only part of the therapy. The scarcity of data makes it difficult to ascertain the beneficial effects of chenodeoxycholic acid in patients with Cerebrotendinous Xanthomatosis.

The choice of chenodeoxycholic acid dosage was empirically derived for all patients based on the normalisation of urine and serum bile acids. No dose response study has been conducted. Hence, it is not possible to ascertain whether the proposed dosing regimen is optimal in the target patient population.

The clinical efficacy of CDCA treatment is more difficult to assess than the biochemical efficacy. A formal comparison of the long term clinical outcome of patients suffering from CTX with and without
CDCA treatment would have been desirable. However, due to the rarity of the disease and the fact that most of the cases presented were detected at a symptomatic stage of differing severity, a formal study would not be feasible.

It is likely that due to the multiple nature of therapy (dietary, pharmaceutical, supportive) in CTX patients, the magnitude of the clinical effects of CDCA treatment may be overestimated.

**Risks**

**Unfavourable effects**

The adverse effects seen with chenodeoxycholic acid therapy appear to be not serious, reversible and mainly related to elevated hepatic enzymes.

**Uncertainty in the knowledge about the unfavourable effects**

In the absence of controlled trial data, it is difficult to ascertain causality of the unfavourable effects. With regards to literature reports, no clear pre-defined observation period on which an incidence calculation may be based is available. Information on the number of patients and the total time of observation was not available in some cases.

**Effects table**

**Table 20: Effects Table for chenodeoxycholic acid in the treatment of CTX.**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Short Description</th>
<th>Unit</th>
<th>Treatment</th>
<th>Control</th>
<th>Uncertainties/ Strength of evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favourable Effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced serum cholestanol</td>
<td>Mean reduction 56.38 to 68.62 µmol/L</td>
<td>µmol/L</td>
<td>CDCA</td>
<td>none</td>
<td>Small, uncontrolled, retrospective studies</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>(Biochemical outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduced excretion of urinary</td>
<td>79% patients improved at current visit</td>
<td>%pt</td>
<td>CDCA</td>
<td>none</td>
<td>Small, uncontrolled, retrospective studies</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>bile acids (Indirect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>biochemical outcome)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved systemic disease,</td>
<td>Diarrhoea-100% improvement, Cognitive</td>
<td>%pt</td>
<td>CDCA</td>
<td>none</td>
<td>Small, uncontrolled, retrospective studies</td>
<td>clinical studies, effects</td>
</tr>
<tr>
<td>CNS signs &amp; symptoms</td>
<td>dysfunction-88.9%, Pyramidal dysfunction – 60%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>supported by literature</td>
</tr>
<tr>
<td></td>
<td>improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological disability score</td>
<td>Stabilisation or improvement in 84.6% and</td>
<td>%pt</td>
<td>CDCA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Rankin and Stabilisation)</td>
<td>76.9% of</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Effect Table

<table>
<thead>
<tr>
<th>Effect</th>
<th>Short Description</th>
<th>Unit</th>
<th>Treatment</th>
<th>Control</th>
<th>Uncertainties/Strength of evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfavourable Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic adverse reactions</td>
<td>N/a</td>
<td>CDCA</td>
<td>None</td>
<td></td>
<td>Known side effect</td>
<td>Clinical studies</td>
</tr>
<tr>
<td>Constipation</td>
<td>N/a</td>
<td>CDCA</td>
<td>None</td>
<td></td>
<td></td>
<td>Clinical studies</td>
</tr>
</tbody>
</table>

%pt- percent of patients

### Benefit-risk balance

#### Importance of favourable and unfavourable effects

Oral CDCA therapy has been shown to restore normal laboratory parameters and significantly improve the affected patients’ symptoms. This reflects restoration of an effective feedback control of bile acid synthesis and a metabolic equilibrium.

The overall safety profile of chenodeoxycholic acid has been found to be favourable.

### Benefit-risk balance

Oral chenodeoxycholic acid appears to be an effective and well tolerated long-term treatment of patients with Cerebrotendinous Xanthomatosis. The use of chenodeoxycholic acid to treat this disease condition has been documented in the literature over a period of approximately 40 years. Due to the extreme rarity of the disease as well as the specialised knowledge and the tools needed for the diagnosis, the number of cases reported in the literature remains limited. However, objectively measurable significant improvements in metabolic and clinical parameters have been demonstrated.

Treatment with chenodeoxycholic acid at appropriate doses produced no significant adverse events, as reported consistently in the literature and retrospective clinical trials.

#### Discussion on the benefit-risk balance

Cerebrotendinous Xanthomatosis is a progressive disease which, if untreated, leads to death from neurological damage. Currently there is no causal treatment. Treatment is limited to correcting the biochemical abnormalities, including the administration of bile acids and vitamin preparations.

Although the data submitted is limited as expected in such rare conditions, it is nevertheless considered that the clinical information presented in this application is adequate to support the demonstration of efficacy and safety of chenodeoxycholic acid in the claimed indication. Taken together, the combined evaluation of the submitted retrospective studies and the published literature provides a significant, albeit not comprehensive, evidence to support the efficacy and safety of chenodeoxycholic acid in patients with Cerebrotendinous Xanthomatosis.

The CHMP was of the opinion that the applicant was unable to provide comprehensive data on the efficacy and safety under normal conditions of use because the indication for which CDCA is intended is encountered too rarely. It would be contrary to generally accepted principles of medical ethics to
collect such information as participation in a controlled trial would expose patients to a risk of liver failure or even death. A marketing authorisation under exceptional circumstances for CDCA is acceptable in regards to the fulfilled criteria of rarity of the disease (the indications for which the product is intended are so rare that the applicant cannot be reasonably expected to provide comprehensive evidence) and medical ethics (it would be contrary to generally accepted principles of medical ethics to collect such information). Monitoring of the patients and collection of long-term efficacy and safety data will be collected via a patient registry.

4. Recommendation

**Similarity with authorised orphan medicinal products**

The CHMP by consensus is of the opinion that Chenodeoxycholic acid sigma-tau (chenodeoxycholic acid) is not similar to Kolbam (cholic acid) and Orphacol (cholic acid) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

**Outcome**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Chenodeoxycholic acid sigma-tau is favourable in the following indication:

Chenodeoxycholic acid sigma-tau is indicated for the treatment of inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency (presenting as cerebrotendinous xanthomatosis (CTX)) in infants, children and adolescents aged 1 month to 18 years and adults.

The CHMP therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

**Conditions or restrictions regarding supply and use**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

**Other conditions and requirements of the marketing authorisation**

**Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.
Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>In order to collect long term safety and efficacy data in patients treated with chenodeoxycholic acid, the MAH will submit the results of a study deriving from a registry of patients with inborn errors of primary bile acid synthesis due to sterol 27 hydroxylase deficiency in infants, children and adolescents aged 1 month to 18 years and adults.</td>
<td>Study results - 1st submission 2022 (and then 5 yearly)</td>
</tr>
</tbody>
</table>

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.