COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ursodeoxycholzuur Sandoz 300 mg and 450 mg, tablets

(ursodeoxycholic acid)

NL/H/4354/001-002/DC

Date: 10 September 2019

This module reflects the scientific discussion for the approval of Ursodeoxycholzuur Sandoz 300 mg and 450 mg, tablets. The procedure was finalised on 14 June 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
PBC	Primary biliary cholangitis
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UDCA	Ursodeoxycholic Acid

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ursodeoxycholzuur Sandoz 300 mg and 450 mg, tablets from Sandoz B.V.

The product is indicated for:

- The dissolution of cholesterol-rich gallstones in patients:
  - who have one or more radiolucent (X-ray negative) gallstones, preferably with a diameter of no more than 15 mm, and a well functioning gallbladder.
  - who refuse surgery or who have surgery contraindicated.
  - who have super-saturation of cholesterol as indicated by chemical investigations of bile, obtained through duodenal probing.

- Primary biliary cholangitis

Paediatric population

- Hepatobiliary disorder associated with cystic fibrosis in children aged 6 years to less than 18 years.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of ursodeoxycholic acid (UDCA). UDCA has been used in clinical practice for over 20 years. In the Netherlands, Ursochol tablets and Ursofalk capsules have been registered since 1979 and 1980, respectively. Also in other European countries, UDCA has been registered for 10-20 years. The use of UDCA in the proposed indications has been sufficiently substantiated and can be considered well-established.

No new (pre)clinical studies were conducted. The MAH submitted non-clinical and clinical overviews based on scientific literature.

The marketing authorisation has been granted pursuant to Article 10a of Directive 2001/83/EC.

The concerned member state (CMS) involved in this procedure was Luxembourg.

Similarity assessment in view of the orphan drug legislation

The MAH provided a similarity assessment versus the orphan medicinal product Ocaliva (obeticholic acid). Obeticholic acid received its orphan designation on 27 July 2010 (EU/3/10/753) for the treatment of Primary Biliary Cholangitis and the European Commission granted a marketing authorisation valid throughout the European Union for Ocaliva on 12 December 2016.

A detailed comparison of the molecular structure, the therapeutic indications and the mechanism of action of ursodeoxycholic acid and obeticholic acid in line with the Commission Communication on assessing similarity of medicinal products versus authorised orphan medicinal products has been presented.
Having considered the arguments presented by the MAH, the member states concluded that the indication and mechanism of action of ursodeoxycholic acid and obeticholic acid are not similar in the context of orphan medicinal products.

II. QUALITY ASPECTS

II.1 Introduction

Ursodeoxycholzuur Sandoz 300 mg is a white round tablet with a smooth surface and a score line. Each tablet contains 300 mg ursodeoxycholic acid. The score line is only to facilitate breaking for ease of swallowing and not to divide into equal doses.

Ursodeoxycholic acid Sandoz 450 mg is a white capsule-shaped (oblong) tablet with a smooth surface. Each tablet contains 450 mg ursodeoxycholic acid.

The tablets are packed in aluminium/PVC blisters.

The excipients are: lactose monohydrate, maize starch, talc, povidone K-30, magnesium stearate

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is ursodeoxycholic acid, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white powder, which is practically insoluble in water, freely soluble in ethanol (96%), slightly soluble in acetone and practically insoluble in methylene chloride. The drug substance is considered to be a BCS class II compound.

The CEP procedure is used for both manufacturers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The specification is in line with the Ph.Eur. monograph, with a number of additional requirements. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches per supplier.

Stability of drug substance

One CEP holder provided stability data on 5 full-scale batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (6 months). No trends or out-of-specification results are observed at accelerated and long term conditions in any of the tested batches. A retest period of 60 months is granted.

The active substance from the second CEP holder is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. For the development of the drug product the MAH characterised Ursochol tablets, which was used as a reference product. Based on this reference product the manufacturing process, a wet granulation process, was chosen with dose-weight proportionate approach followed by compression. The UDCA Sandoz 450 mg tablet is manufactured using the same common blend as in the UDCA Sandoz 300 mg tablets manufacturing, hence no specific manufacturing development is needed.

Dissolution tests were provided comparing the reference product with the proposed product at pH 1.2 and pH 4.5. In both media 0% dissolution was found after 8 hours. Based on this finding dissolution tests at pH 1.2 and 4.5 were not carried out for comparative dissolution study.

Instead the dissolution tests were evaluated at pH 6.8, 7.5 and 8.0 media. The obtained results demonstrated that the similarity factor is always more than 50 at all three pH values. Based on all dissolution data it can be considered that test and reference tablets can be considered to be similar with respect to dissolution. Based on the provided information the product is pharmaceutically equivalent to the reference product.

Manufacturing process

The manufacturing process is a wet granulation process followed by compression into tablets. The manufacturing process has been adequately validated according to relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation data on the product has been presented for three full-scale batches per strength.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average weight, uniformity of dosage units, disintegration, loss on drying, identification, assay, related substances, dissolution and microbiological enumeration tests and tests for specified microorganisms.
The release and shelf-life requirements/limits are identical with exception of the average weight, uniformity of dosage units, disintegration, and the identification of UDCA. These tests are not included in the shelf life specifications. The analytical procedures have been adequately validated.
The dissolution limit of not less than 85% (Q=80%) of labelled amount of drug is dissolved in 30 minutes is acceptable and in line with the 'Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action'.
Batch analytical data from the proposed production site have been provided on three full-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three full-scale batches of the 300 mg strength and three pilot-scale batches of the 450 mg strength stored at 25°C/60% RH (up to 36 months), 30°/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC-Al Blister pack. At the end of the shelf life the batches complied with the specification requirements.
Based on the provided stability data the proposed shelf life of 36 months has been granted. At photolytic conditions no degradation was observed. No special storage conditions are required.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ursodeoxycholzuur Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

Ursodeoxycholic acid (UDCA) is a naturally occurring, physiologic, hydrophilic bile acid, derived from cholesterol. It is used clinically for its cholelitholytic and anticholestatic action.
The nonclinical overview reviewed available literature on pharmacology, pharmacokinetics and toxicology of UDCA. These data show that it is a well-known medicinal substance. The effect of UDCA in hepatic and cholestatic diseases is thought to be due to a relative exchange of lipophilic, detergent-like, toxic bile acids for the hydrophilic, cytoprotective, non-toxic ursodeoxycholic acid, to an improvement in the secretory capacity of the hepatocytes, and to immune-regulatory processes.
UDCA showed beneficial effects on the histological, biochemical, and hemodynamic abnormalities induced by bile duct ligation in rats. Non-clinical data on toxicological properties of ursodeoxycholic acid reveal no special hazard for humans in addition to what is known from clinical experience. The member states agreed no further non-clinical studies are required.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Ursodeoxycholic acid is a well-known active substance. Several medicinal products are already on the market containing UDCA as the active substance, at the same or similar strengths, and are registered for the same indication. An increase in use and therefore environmental exposure is unlikely. An environmental risk assessment is therefore not deemed necessary.

III.3 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of ursodeoxycholic acid are well known. The MAH has not provided additional studies and further studies are not required.

IV. CLINICAL ASPECTS

IV.1 Introduction

UDCA is a well-known active substance with established efficacy and tolerability.
The dossier is based on well-established use of UDCA. The MAH submitted a clinical overview for the justification of the proposed indications and posology. Sufficient literature references were provided.

IV.2 Pharmacokinetics

The MAH submitted an overview of literature data on the pharmacokinetics of UDCA. UDCA is a well know drug and the general overview on the pharmacokinetics is considered sufficient.
UDCA is a bile acid which causes a reduction in cholesterol in biliary fluid. After oral administration, UDCA (an endogenous compound) dissolution in the proximal jejunum takes place through solubilisation in small micelles with other bile acids. UDCA is only absorbed systemically to a small extent and is considered not to act systemically. However, UDCA levels can be used to show a comparable absorption of UDCA from different formulations.

For bridging, the MAH demonstrated that the formulation is comparable to Ursochol, 300 and 450 mg tablets, containing crospovidon, lactose, povidone and Mg stearate. Both formulations do not contain critical excipients. Furthermore, the MAH refers to a study of Williams et al.[1] in its overview. This study showed pharmacokinetics of 4 different UDCA formulations. The data indicate that the small differences in composition between Ursodeoxycholic acid Sandoz 300 and 450 mg tablets and the Ursochol 300 and 450 mg tablets (and Ursofalk 250 mg capsules) are unlikely to affect the absorption in a clinically relevant way.
Comparative dissolution studies at pH 6.8, 7.5 and 8.0 were conducted on three UDCA 300 mg batches and UDCA 450 mg batches and one Ursochol 300 mg batch and Ursochol 450 mg batch. The obtained results demonstrated that the similarity factor is always more than 50 at all three pH values. Based on all dissolution data it can be considered that UDCA Sandoz 300 mg tablets and Ursochol 300 mg tablets and UDCA Sandoz 450 mg tablets and Ursochol 450 mg tablets can be considered to be comparable with respect to dissolution.
Taking into account the differences in composition between the UDCA Sandoz 300 and 450 mg tablets and Ursochol 300 and 450 mg tablets, the comparable dissolution at pH 6.8, 7.5 and 8.0 and the provided literature data on pharmacokinetics from different UDCA formulations, a clinically relevant difference in bioavailability is not expected. The MAH has sufficiently supported that the data obtained with the different formulations as described in the submitted literature data can be bridged to the current formulation.

IV.3 Pharmacodynamics

In patients with primary biliary cholangitis (PBC), several different mechanisms have been shown for efficacy of UDCA therapy. One of the main therapeutic mechanisms of UDCA is displacement of other, more hydrophobic and therefore toxic endogenous bile acids by expansion of the hydrophilic bile acid pool. Additional mechanisms include cytoprotective effects on hepatocytes and bile duct epithelial cells, immunomodulatory and anti-apoptotic effects, and stimulation of bile secretion by hepatocytes and bile duct epithelial cells. In hepatobiliary disorder with cystic fibrosis patients, UDCA is known to stimulate HCO3-

[1] Williams CN, Al-Knawy B, Blanchard W. Bioavailability of four ursodeoxycholic acid preparations. Aliment Pharmacol Ther 2000; 14; 1133-1139.

secretion, which is impaired due to a mutation of the cystic fibrosis transmembrane regulator gene.
The MAH submitted a good and concise overview reflecting the currently known data on the pharmacodynamics of UDCA. The information is adequately reflected in the proposed SmPC.

IV.4 Clinical efficacy

The MAH provided a concise overview of the scientific literature to substantiate the indications stated in the SmPC. The application contains an adequate review of published clinical data. No new studies have been performed and none are required for this type of application.

Although limited literature has been submitted to substantiate the indication 'Hepatobiliar disorder associated with cystic fibrosis in children aged 6 years to less than 18 years', the indication is approvable, as it was approved in a paediatric worksharing procedure (UK/W/036/pdWS/001).

Within the SmPC the paediatric worksharing procedure (UK/W/036/pdWS/001) and the CSP (MT/H/PSUR/0001/002) are implemented. The SmPC is generally in line with that of Ursochol.

IV.5 Clinical safety

Diarrhoea is the most common adverse effect observed with UDCA therapy. UDCA is known to be least hepatotoxic amongst the available bile acids, however, decompensation of liver cirrhosis has been observed rarely in cases of advanced PBC. Calcification of gallstone, though rarely, has been observed with UDCA treatment. Rarely, abdominal pain, pruritus, urticaria and weight gain may occur. If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued.

Contraindications to UDCA therapy include any hypersensitivity to bile acids or any other excipients, acute inflammation of the gall bladder or biliary tract, occlusion of the biliary tract, frequent episodes of biliary colic, radio-opaque calcified gallstones, and impaired contractility of the gall bladder. In order to assess therapeutic progress and for timely detection of any calcification of the gallstones, depending on stone size, the gall bladder should be visualised (oral cholecystography) with overview and occlusion views in standing and supine positions (ultrasound control) 6-10 months after the beginning of UDCA treatment for gallstone dissolution. If the gall bladder cannot be visualised on X-ray images, or in cases of calcified gallstones, impaired contractility of the gall bladder or frequent episodes of biliary colic, UDCA should not be used.

It is suggested that other therapy be considered if the patient is not free of stones within 24 months, as the risk of calcification of the gall stones is increased with the duration of treatment. The liver function parameters including AST, ALT and L-glutamyltransferase should be monitored by the physician every 4 weeks, during the first 3 months of treatment,

thereafter every 3 months. Apart from allowing for identification of responders and non-responders in patients being treated for PBC, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advanced stage PBC. Rarely, in patients with PBC, the clinical symptoms may worsen at the beginning of treatment, e.g. itching may increase. In very rare cases decompensation of hepatic cirrhosis has also been observed in patients with PBC on UDCA treatment, which partially regressed after the treatment was discontinued.

The adverse drug reactions, warnings and contraindications have been adequately described in the SmPC.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ursodeoxycholzuur Sandoz.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Hepatic decompensation in primary biliary cirrhosis • Diarrhoea • Biliary colic • Hypersensitivity and skin reactions
Important potential risks	• Teratogenicity
Missing information	• Off label use in patients with radio-opaque calcified gallstones, occlusion of biliary tract, frequent episodes of biliary colic and impaired contractility of gall bladder • Off label use in patients with acute inflammation of the gall bladder or biliary tract • Safety in breast-feeding

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

UDCA has been used and is registered for the requested indications in Europe for 10-20 years. Based upon clinical data and the longstanding clinical experience, the use of UDCA in the proposed indications can be considered well-established with demonstrated efficacy.
The safety profile of UDCA in the proposed indications is considered well-established and acceptable. The adverse events of UDCA are well characterised and adequately covered by the SmPC. The member states agreed no further clinical studies are required.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. No problems were identified regarding comprehensibility and usefulness of the information and thus no amendments were made during the two rounds of testing. However, as a result of the general comments made, one clarification was made in the text to explain a difficult medical term. Altogether the testing has been adequately performed. The final leaflet is considered acceptable from a readability point of view, with patients/users being able to act properly upon the information that it contains. The results of the user test show that the PL 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ursodeoxycholzuur Sandoz 300 mg and 450 mg, tablets have a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

From a clinical point of view, the proposed indications are in line with current ursodeoxycholic acid use and recommendations. UDCA has been registered in Europe for over 10 years. Based upon clinical data and the longstanding clinical experience, the use of UDCA in the proposed indications can be considered well-established with demonstrated efficacy and acceptable safety.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that well-established use has been demonstrated for this medicinal product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 June 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse