CBG MEB

Public Assessment Report

Scientific discussion

Ursosan 250 mg, hard capsules

(ursodeoxycholic acid)

NL/H/3897/001/DC

Date: 6 November 2018

This module reflects the scientific discussion for the approval of Ursosan 250 mg, hard capsules. The procedure was finalised on 4 January 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ursosan 250 mg, hard capsules from Kappler Pharma Consult GmbH.

The product is indicated for:
- dissolution of cholesterol gallstones of the gall bladder. The gallstones must not produce any shadows on the radiograph and should not be of a greater diameter than 15 mm, and the gall bladder, despite the gallstone(s), must be functioning.
- treatment of gall reflux gastritis.
- symptomatic treatment of primary biliary cholangitis (PBC, as long as there is no decompensated cirrhosis of the liver.
- treatment of hepatobiliary disorders associated with cystic fibrosis in children aged 6 to 18 years (paediatric population).

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Ursofalk 250 mg hard capsules which has been centrally registered in the EEA by Dr. Falk Pharma since 15 March 1999. The Dutch reference product is Ursofalk 250 mg capsules from Dr. Falk Pharma Benelux B.V. (NL Licence RVG 08384, date of authorisation: 14 November 1980).

The concerned member states (CMS) involved in this procedure were Austria, Denmark and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

Similarity assessment in view of the orphan drug legislation
The MAH provided a similarity assessment report 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 PBC and the European Commission granted a marketing authorisation valid throughout the European Union for Ocaliva on 12 December 2016.
It is concluded that, having considered the arguments presented by the MAH of ursodeoxycholic acid, 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

Ursosan is a white, hard gelatine capsules containing white or almost white powder.

Each hard capsule contains 250 mg of ursodeoxycholic acid (UDCA).

The capsules are packed in PVC-PVDC/Al blisters.

The excipients are maize starch, pregelatinised maize starch, colloidal anhydrous silica (E551), magnesium stearate (E470b), gelatin (E441) and titanium dioxide (E171).

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 white or almost white powder and is practically insoluble in water. No polymorphic forms of ursodeoxycholic acid are known.

The CEP procedure is used for 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 active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for 13 full scale batches.

Stability of drug substance
The active substance is stable for 36 months or 60 months, depending on the manufacturer, 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients justified and their functions explained. All excipients used are well known. The choice of packaging material and manufacturing process is justified.
Three bioequivalence studies have been submitted. The test product batch used in the pivotal bioequivalence study has the same composition as the intended commercial batches. Data on comparative dissolution testing at three pHs, and the QC release medium of the batches of test and reference product used for bioequivalence studies have been included. The addition of 0.01% sodium lauryl sulphate (SLS) to the routine dissolution medium, according to the used United States Pharmacopoeia (USP) method, is sufficiently justified.

Manufacturing process
The manufacturing process for the drug product includes mixing and wet granulation, drying, sieving, lubrication, filling of the capsules and packaging. It is considered a standard manufacturing process and has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for seven batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph.Eur. and in house requirements. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mass of the capsule content, uniformity of dosage units, disintegration time, identification, purity, assay, dissolution and microbiological limits. The release and shelf-life limits for all parameters are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from six commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for four smallest production scale batches and five maximum production scale batches stored at 25°C/60% RH (60, 48, 24 or 12 months), 30°C/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 the proposed packaging. Under all three storage conditions no out of specification results or significant changes have been observed in any of the parameters tested. No specific up- or downward trends are seen. Results on photostability studies

were submitted and no changes were observed. On basis of the data submitted, a shelf life was granted of 48 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

The drug substance is manufactured from animal material, and the TSE safety is either covered by the CEPs or by separate declarations of the manufacturers regarding the manufacturing process and the origin of the source materials.
TSE-CEP's have been provided for the gelatin used in the capsule shell.
For the other excipients statements with respect to TSE safety are provided except for titanium dioxide, however the latter is not considered a risk material.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ursosan 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 Ecotoxicity/environmental risk assessment (ERA)

Since Ursosan is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Ursofalk which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ursodeoxycholic acid is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted three bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies
The first bioequivalence study was an open label, two-period, two-sequence, two-way crossover, controlled, randomised, single dose bioequivalence study of Ursosan 250 mg, capsules (test formulation) vs. and equal dose of Ursofalk capsules (reference formulation) in 66 healthy male and female volunteers under fasting conditions. The sampling schedule, sampling period and washout period were found not to be adequate for the purpose of this study. Moreover, validity of the analytical method was found questionable with a major concern relating to the lower limit of quantification (LLOQ) and resulting acceptability of analytical runs. In conclusion, bioequivalence was not considered to have been demonstrated indisputably through this study.
The second bioequivalence study was an open label, two-period, two-sequence, two-way crossover, randomised, single dose bioequivalence study of Ursosan 250 mg capsules vs. an equal dose of Ursofalk capsules (reference formulation) in healthy male and female volunteers under fasting conditions. Major concerns were raised regarding this new study and a Good Clinical Practice (GCP) inspection of this trial was requested. Based on the negative outcome of the GCP inspection and previous assessment, it was concluded that the study is not acceptable for demonstration of bioequivalence.

Considering the critical and major findings for the first two studies, only the third study will be elaborately discussed in this report.

Design
An open label, single dose, randomised, two-period, two-sequence, two-treatment crossover bioequivalence study was carried out under fasted conditions in 66 healthy subjects (43 males, 23 females), aged 18-55 years. Each subject received a single dose (500 mg; 2x 250 mg capsules) of one of the two ursodeoxycholic acid formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of 29 days.

Blood samples were collected at day -1 at -24, -20, -16, -14, -12, -8 hours and at day 1 at pre-dose and at 0.083, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC of the reference product, the capsules should be taken unchewed with some liquid. As such, the fasting condition applied in the study is considered adequate. It has to be noted that in the Dutch SmPC the capsules should be taken with food. The washout period of 29 days and sampling period of 72 hours are acceptable.
Pre-dose sampling was needed in order to determine baseline plasma concentrations of endogenous ursodeoxycholic acid and adjustment of post dose concentration was performed by standard subtractive method.
The decision of administering a dose of 500 mg (2x 250 mg) of ursodeoxycholic acid was taken in order to reduce the occurrence of low concentrations (bellow LLOQ) values that might influence the calculation of post-dose AUC, which is acceptable.

The choice of the reference product
The choice of the reference product (Urosfalk 250 mg capsules) in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Two subjects dropped-out for personal reasons (family related), one subject dropped-out as the subject didn't show up for the second period, and one subject was withdrawn from the study at the decision of the clinical investigator, because in the washout period the subject applied for a job

position in the organisation and to avoid ethical conflict the clinical investigator decided to withdrawn the subject from the study. Therefore, 62 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ursodeoxycholic acid under fasted conditions.

Treatment N=62	AUC_{0-t} ng.h/ml	AUC_{0-t} ng.h/ml Baseline corrected	C_{max} ng/ml	C_{max} ng/ml Baseline corrected	t_{max} h
Test	32087 ± 14544	29634 ± 13289	5277 ± 2984	5243 ± 2990	2.0 (0.5 – 5.0)
Reference	33130 ± 15346	30395 ± 13882	5141 ± 2852	5104 ± 2857	2.0 (0.5 – 5.0)
***Ratio (90% CI)**	0.97 (0.90 - 1.06)	0.98 (0.90 – 1.07)	1.04 (0.94 – 1.15)	1.04 (0.94 – 1.15)	
CV (%)	27.5	1.04	34.4	34.8	

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Safety
Seventeen adverse events out of which eleven of moderate intensity and six of mild intensity occurred in seven subjects in the present study. These were not serious adverse events. The volunteers that encountered the adverse events completely recovered before the end of the study.

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ursosan 250 mg is considered bioequivalent with Ursofalk 250 mg.

The MEB has been assured that the third bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 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 Ursosan.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Drug-induced gastro-intestinal disorders (diarrhoea) • Biliary colic • Decompensation of hepatic cirrhosis in patients with advanced stage of primary biliary cirrhosis • Hypersensitivity and skin reactions
Important potential risks	• Teratogenicity
Missing information	• Off-label use in patients with radio-opaque calcified gallstones, occlusion of the biliary tract, frequent episodes of biliary colic and impaired contractility of the gall bladder or the biliary tract • Off-label use in patients with acute inflammation of the gall bladder or biliary tract • Off-label use in children with biliary atresia

	• Use in breastfeeding women

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

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Ursofalk. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has (PL) been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ursosan 250 mg, hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Ursofalk 250 mg hard capsules. Ursofalk is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 essential similarity has been demonstrated for Ursosan with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 4 January 2018.

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