COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ursonorm 500 mg film-coated tablets

(ursodeoxycholic acid)

NL/H/3991/001/DC

Date: 29 October 2018

This module reflects the scientific discussion for the approval of Ursonorm 500 mg film-coated tablets. The procedure was finalised on 9 May 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

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
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 Ursonorm 500 mg film-coated tablets, from PRO.MED.CS Praha a.s.

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.
- 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.

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 European reference product Ursofalk 500 mg tablets which has been registered in Germany since 15 March 1999 by Dr. Falk Pharma. The justification to use this product is based on information received from Germany.

The concerned member states (CMS) involved in this procedure were Belgium, Estonia, Finland, Ireland, Lithuania, Luxembourg, Latvia, Slovenia and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Ursonorm is a almost white, oblong film-coated tablet with a break line on each side. Each tablet contains 500 mg of ursodeoxycholic acid (UDCA) as the active ingredient and can be divided into equal doses.

The film-coated tablets are packed in PVC-PVDC/Al blisters.

The excipients are:
Tablet core - maize starch, pregelatinised maize starch, sodium starch glycolate A (E468), silica colloidal anhydrous (E551) and magnesium stearate (E470b)
Tablet coating - hypromellose 6 (E464), titanium dioxide (E171) and macrogol 400

II.2 Drug Substance

The active substance is ursodeoxycholic acid, an established active substance described in the European Pharmacopoeia (Ph. Eur). Ursodeoxycholic acid is a white or almost white powder and practically insoluble in water and freely soluble in ethanol (96%). The Ph. Eur. does not report the existence of polymorphism.

The CEP procedure is used for the active substance; a total of six CEPs are included. 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 European Pharmacopoeia.

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 and meets the requirements of the monograph in the Ph.Eur. with additional limits for related substances, related solvents, residual reagents and loss on drying as mentioned on the CEPs. An adequate description of the in-house method used to control residual solvents has been provided. Batch analytical data demonstrating compliance with this specification have been provided.

Stability of drug substance

The proposed retest period differs between the CEPs and varies between 36 months and 60 months. Therefore, different retest periods for the active substance are adopted by the MAH.

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 is justified and their functions explained. A bioequivalence study is carried out between the test product Ursonorm 500 mg film-coated tablets and the reference product Ursofalk. Comparative dissolution profiles of the test and the reference product batches have been provided at four different pH values. The tablets did not dissolve in 0.1M HCl and phosphate buffer pH 4.5. The dissolution profiles of the test and reference batch are visually similar. The proposed QC medium is phosphate buffer pH 8.0. Overall, the pharmaceutical development is acceptable.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines and consists of weighing and sieving, pre-granulation blending, preparation of the binding solution, granulation, drying and sieving, blending, compression, coating and packaging. It is considered to be a standard process. Process validation data on the product have been presented for three pilot scaled batches and three production scaled batches in accordance with the relevant European guidelines.

Control of excipients

With the exception of the Opadry film-coating, all excipients comply with their respective Ph. Eur. monograph. For the Opadry film-coating an in-house specification is included. 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 tablet, uniformity of dosage units (mass variation), identification, purity, assay, dissolution and microbiological quality. 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 four pilot scaled batches from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for four pilot scaled batches stored at 25°C/60 % RH (60 months) and 40°C/75% RH (6 months). One batch was stored at 30°C/65% RH (12 months). The conditions is the study have been performed under ICH storage conditions. All tested parameters for all tested storage conditions remained within the specification. No significant changes and no up- or downward trends have been observed, only some minor analytical variation is seen. Results of a photostability study indicate that the product is photostable. On the basis of the provided stability data, the claimed shelf-life of 48 months without any special storage conditions can be granted.

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.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ursonorm 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 Ursonorm 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ursonorm 500 mg film-coated tablets (PRO.MED.CS Praha a.s., Czech Republic) is compared with the pharmacokinetic profile of the reference product Ursofalk 500 mg tablets (Dr. Falk Pharma, Germany).

The choice of the reference product in the bioequivalence study is accepted. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy (21 male and 23 female) subjects, aged 18-53 years. Each subject received a single dose (500 mg) of one of the 2 ursodeoxycholic acid formulations. The tablet was orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 29 days.

Blood samples were collected at pre-dose and 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 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, the tablets should be swallowed with some liquid and the tablets should not be crushed or chewed. As such, the fasting condition applied in the study is considered adequate.

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

Four subjects were considered drop-out in this study as they all dropped-out for personal reasons before the second period. Therefore, 40 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=40	**AUC_{0-72h}** ng.h/ml	**C_{max}** ng/ml	**AUC_{0-72h}** ng.h/ml (baseline corrected)	**C_{max}** ng/ml (baseline corrected)	**t_{max}** h
Test	26912 ± 13960	3717 ± 1400	24505 ± 12555	3683 ± 1397	2.5 (0.5 – 18.0)
Reference	25092 ± 12628	3438 ± 1121	23101 ± 11712	3410 ± 1120	2.0 (0.25 – 18.0)
***Ratio (90% CI)**	1.06 (0.97 - 1.16)	1.06 (0.96 - 1.17)	1.04 (0.96 – 1.15)	1.06 (0.96 – 1.15)	--
CV (%)	23.9	27.1	24.6	27.3	--

$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to 72 hours
C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ursonorm is considered bioequivalent with Ursofalk

The MEB has been assured that the 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 Clinical efficacy

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.
- 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.

The MAH proposed the indications from the SmPC of the innovator product Ursofalk (DE), except for the indication "*treatment of gall reflux*". This is acceptable as the indication "*treatment of gall reflux gastritis*" is not registered in the Netherlands. The innovator SmPC was been last updated in 2016 (which also takes into account the paediatric worksharing procedure (UK/W/036/pdWS/001) and the CSP (MT/H/PSUR/0001/002).

The indications "*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*" and "*primary biliary cirrhosis*" are acceptable. However, given the recent nomenclature chance of primary biliary cirrhosis to primary biliary cholangitis by major hepatology societies and advocacy groups, the RMS requested the MAH to amend the indications as follows: "*…. primary biliary cholangitis …*".

IV.4 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 Ursonorm.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Diarrhoea - Biliary colic - Decompensation of hepatic cirrhosis in patients with advanced stage of primary biliary cirrhosis
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 - Off-label use in patients with acute inflammation of the gall bladder or biliary tract - Off-label use in children with biliary atresia following unsuccessful portoenterostomy or without recovery of good bile flow - Safety in breastfeeding

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

IV.5 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Ursosan 500 mg film-coated tablets, NL/H/3897/001/DC. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ursonorm 500 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Ursofalk 500 mg tablets. 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 Ursonorm with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 May 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