COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ursonorm 400 mg film-coated tablets

(ursodeoxycholic acid)

NL/H/3991/002/DC

Date: 16 December 2021

This module reflects the scientific discussion for the approval of Ursonorm 400 mg film-coated tablets. The procedure was finalised at 6 September 2021. 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
ERP	European Reference Product
FXR	Farnesoid X Receptor
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
OCA	Obeticholic Acid
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 Ursonorm 400 mg film-coated tablets, from Pro.Med.Cs Praha a.s.

The product is indicated:

- For the dissolution of cholesterol gallstones in the gall bladder. The gallstones must not show as shadows on X-ray images and should not exceed 15 mm in diameter. The gall bladder must be functioning despite the gallstone(s).
- For symptomatic treatment of primary biliary cholangitis (PBC), provided there is no decompensated hepatic cirrhosis.
- For 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 hybrid application claiming essential similarity with the European reference product Ursofalk 500 mg film-coated tablets, which has been registered in Germany by Dr. Falk Pharma since 15 March 1999. The justification to use this product is based on information received from Germany.

This application concerns a line extension to the already approved product Ursonorm 500 mg film-coated tablets (NL License RVG 120610). In the Netherlands, these Ursonorm 500 mg strength tablets, from the same Marketing Authorisation Holder (MAH), have been authorised since July 2018 through a decentralised procedure (NL/H/3991/001).

The concerned member states (CMS) involved in this procedure were Belgium, Finland, Ireland, Luxembourg and United Kingdom (Northern Ireland).

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as the product has the same pharmaceutical form and composition as the ERP but different strength.

<u>Similarity assessment in view of the orphan drug legislation</u>
The MAH provided a similarity report in which potential similarity between Ursonorm 400 mg film-coated tablets and Ocaliva were discussed. Currently, Ocaliva has market exclusivity for the indication: treatment of primary biliary cholangitis. Based on the data in the report, the therapeutic indications of Ursonorm and Ocaliva are considered not similar as Ursonorm is a first line treatment while Ocaliva is a second line treatment. Also the mechanism of action is considered not similar as the obeticholic acid (OCA), which is the active substance of Ocaliva, is an agonist of the farnesoid X receptor (FXR). Ursodeoxycholic acid (UDCA) is known not to have FXR agonist activity but rather acts through post-translational mechanisms. Activation of FXR in the liver reduces conversion of cholesterol to bile acids by down-regulating the primary enzymes involved in bile acid synthesis. OCA induces transcriptional effects, thus augmenting

the properties of UDCA. Therefore, Ursonorm 400 mg tablets are considered not similar to Ocaliva. The indications for Ursonorm 400 mg film-coated tablets are not infringing the market exclusivity of any Orphan Medicinal products with granted marketing authorisation.

II. QUALITY ASPECTS

II.1 Introduction

Ursonorm 400 mg are film-coated tablets. The tablets are almost white, round biconvex and film-coated, with a score line on both sides. The tablets can be divided into equal doses. Each tablet contains as active substance 400 mg of ursodeoxycholic acid (UDCA).

The tablets are packed into PVC/PVdC/Alu blisters.

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

All excipients comply with the Ph. Eur., except for the Opadry film-coating. The excipients and packaging are well known and usual for this type of dosage form.

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 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. 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.

<u>Manufacturing process</u>
A CEP has 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 is in line with the monograph in the Ph. Eur. The specification limits are in compliance with the limits stated in the Ph. Eur., with an additional limit for one residual solvent as mentioned on the CEP. With regard to impurities, Ph. Eur. reference standards are used, except for one impurity, for which the United States Pharmacopeia (USP) reference standard is used. This is considered acceptable.

Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
The active substance 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 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 are explained. A biowaiver of strength is requested in relation to the already approved 500 mg strength. The medicinal product is manufactured by the same manufacturing process (wet granulation), the qualitative composition is the same and the composition of the strengths are quantitatively proportional. Comparative dissolution profiles of batches of the 400 mg and 500 mg strengths have been provided at four different pH values. The tablets did not dissolve in 0.1M HCl and acetate buffer pH 4.5. The dissolution profiles of the batches of the two different strengths are visually similar.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. The process 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 scale batches in accordance with the relevant European guidelines. A validation protocol for the validation of the manufacturing process of full scale batches has been provided and is deemed acceptable. Confirmation that process validation will be performed on the first three commercial scale batches is provided.

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. The tests for identification and uniformity of dosage units are not performed during stability studies. The finished product specification is considered to be acceptable. A risk evaluation concerning the presence of nitrosamine impurities in the drug product is provided and, based on the available information, the conclusion that no risk is identified and no further control on nitrosamines is necessary is endorsed. 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 three pilot 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 three pilot scale batches, in accordance with applicable European guidelines. The product was packed in the commercial packaging of transparent PVC/PVdC foil covered with aluminium foil. The batches were stored for 24 months at 25°C/60%, for 12 months at 30°C/65% and for six months at 40°C/75% RH. The stability studies have been performed under ICH storage conditions and the results of all tested parameters for all tested storage conditions remained within the specifications. A photostability study was performed in accordance with ICH recommendations and showed that the product is photostable. On basis of the data submitted, a shelf life was granted of three years. No specific storage conditions need to be included in the SmPC or on the label.

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 400 mg 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 400 mg is intended for hybrid 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 hybrid formulation of Ursofalk 500 mg film-coated tablets, 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 hybrid application, the MAH has submitted one bioequivalence study, using a 500 mg test and reference product. A justification for a biowaiver has been provided for the 400 mg of the proposed product. Both are 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 film-coated tablets (Dr. Falk Pharma GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the test and reference product.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The MAH applied for a biowaiver for the lower strength of 400 mg film-coated tablets. The test product strength is manufactured by the same manufacturing process (wet granulation), the qualitative composition is the same and the composition of both strengths are quantitatively proportional. Comparative dissolution profiles of the batches of both strengths have been provided at four different pH values. The dissolution profiles of the batches of the two different strengths are visually similar. Additional data provided are considered adequate to support the linearity of UDCA in the range 400 – 500 mg. In conclusion, a biowaiver for the 400 mg strength is applicable.

Bioequivalence study

Design

A single-dose, randomised, two-period, crossover bioequivalence study was carried out under fasted conditions in 44 healthy subjects, aged 18-53 years. Each subject received a single dose (500 mg) of one of the two UDCA 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. In bioequivalence studies with endogenous substances, it cannot be directly assessed whether carry-over has occurred, so extra care must be taken to ensure that the washout period is of an adequate duration. Because of a relatively long half-life of UDCA (3.5-5.8 days) the washout period of 29 days is acceptable.

Blood samples were collected at day -1 at -24, -20, -18, -16, -14, -12 and -8 hours and at day 1 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. Pre-dose sampling was needed in order to determine baseline plasma concentrations of endogenous UDCA and adjustment of post dose concentration was performed by standard subtractive method. UDCA undergoes enterohepatic circulation leading to a long elimination half-life. According to the CHMP Guideline on the Investigation of Bioequivalence, a sampling period longer than 72 h is not considered necessary for any immediate release formulation irrespective of the half-life of the drug. In compliance with this recommendation the duration of sampling up to 72 hours post dose is acceptable.

The design of the study is acceptable.

Ursodeoxycholic acid may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ursodeoxycholic acid. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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 dropped out, all for personal reasons (job or family related). The remaining 40 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (baseline corrected 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)**	**t_{max} (h)**
Test	24505 - 12555	3683 - 1397	2.5 (0.5 – 18.0)
Reference	23101 - 11712	3410 - 1120	2.0 (0.25 – 18.0)
***Ratio (90% CI)**	1.04 (0.96 - 1.15)	1.06 (0.96 - 1.15)	-
CV (%)	24.6	27.3	-

AUC_{0-72h} area under the plasma concentration-time curve from time zero to t 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_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Ursonorm 500 mg film-coated tablets are considered bioequivalent with Ursofalk 500 mg film-coated tablets.

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 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.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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 Ursonorm 500 mg film-coated tablets is similar to the pharmacokinetic profile of the reference product. A biowaiver has been granted for the 400 mg product. Risk management is adequately addressed. This hybrid 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 Ursonorm 500 mg film-coated tablets (NL/H/3897/001/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ursonorm 400 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a hybrid form of Ursofalk 500 mg film-coated 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 400 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 September 2021.

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