CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ursofalk 50 mg/ml suspension
Dr. Falk Pharma Benelux B.V., the Netherlands

ursodeoxycholic acid

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB.
It reflects the scientific conclusion reached by the MEB at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

Registration number in the Netherlands: RVG 101647

12 December 2013

Pharmacotherapeutic group:	bile acid preparations
ATC code:	A05AA02
Route of administration:	oral
Therapeutic indication:	dissolution of cholesterol gallstones; biliary cirrhosis (PBC); adjuvant medication in lithotripsy; treatment of chronic mild to moderate hepatobiliary disorders due to cystic fibrosis in children and adolescents
Prescription status:	prescription only
Date of authorisation in NL:	18 December 2012
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Ursofalk 50 mg/ml suspension from Dr. Falk Pharma Benelux B.V. The date of authorisation was on 18 December 2012 in the Netherlands.

The product is indicated for

- dissolution of cholesterol gallstones
- adjuvant medication in lithotripsy
- primary biliary cirrhosis (PBC)
- treatment of chronic (≥ 6 months) mild to moderate hepatobiliary disorders due to cystic fibrosis in children and adolescents.

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

Ursodeoxycholic acid (UDCA) is a bile acid which effects a reduction in cholesterol in biliary fluid primarily by dispersing the cholesterol and forming a liquid-crystal phase. UDCA affects the enterohepatic circulation of bile salts by reducing the reabsorption in the intestine of endogenous more hydrophobic and potentially toxic salts such as cholic and chenodeoxycholic acids.

In-vitro studies show that UDCA has a direct hepatoprotective effect and reduces the hepatotoxicity of hydrophobic bile salts.

This national procedure concerns a line extension to Ursofalk 250 mg capsules (NL License RVG 08384) which have been registered in the Netherlands by Dr. Falk Pharma Benelux B.V. since 14 November 1980. With this application an additional immediate-release pharmaceutical form is introduced: an oral suspension in addition to the previously authorised capsules.

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

This type of application refers to a full application containing a known active substance. Reference is made to the non-clinical and clinical studies performed with Ursofalk capsules. Moreover the MAH submitted a single and multiple dose study over 14 days with the 50 mg/ml suspension under fasting conditions versus 2 reference UDCA capsule formulations. Furthermore, biliary acid composition and biliary hydrophobicity index (pharmacological effect) were evaluated. In addition the product has been compared to Urso 250 mg tablets from the US market. The results and assessment are discussed in section II.3 ‘Clinical aspects’.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a line extension.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is ursodeoxycholic acid (UDCA), 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, slightly soluble in acetone and practically insoluble in methylene chloride. The active substance is an optical pure enantiomer.

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 European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the CEP and additional requirements for the particle size.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for 3 full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 12 full-scale batches stored at room temperature. No significant changes were detected during 5 years.
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Ursofalk oral suspension contains as active substance 50 mg/ml of ursodeoxycholic acid. It is a white, homogenous suspension containing small air bubbles and with a lemon odour.

The suspension is packed in amber glass bottles with a child-resistant screw cap. Enclosed is a measuring cup (PP) with four graduations: 1.25 ml (= 62.5 mg UDCA), 2.5 ml (= 125 mg UDCA), 3.75 ml (= 187.5 mg UDCA) or 5 ml (= 250 mg UDCA) can be administered.

The excipients are: benzoic acid, citric acid, glycerol, cellulose microcrystalline, carboxymethyl cellulose, sodium chloride, sodium citrate, sodium cyclamate, propylene glycol, purified water, xylitol, lemon flavouring.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The active substance is used in a fine dispersion, to achieve good re-suspendability and dissolution. The bitter taste of UDCA is corrected. As the product is used in a multidose container, benzoic acid is added as a preservative. The efficacy of the amount of benzoic acid has been shown by a challenge test. On the basis of the obtained results of testing, the uniformity of dosage of the intended measuring spoons is considered sufficient.

Manufacturing process
All excipients (except flavour and propylene glycol) are mixed and homogenised. In the next step UDCA is added to the suspension and mixed up. Finally the flavouring, dissolved in propylene glycol is dispersed in the suspension.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 full-scale batches.

Control of excipients
The excipients comply with the European pharmacopoeia and the USP/NL except for the flavour. For the flavour an acceptable specification is provided. The quantitative composition of the flavour has been disclosed.

Quality control of drug product
The product specification includes tests for appearance, identity, assay, degradation, particle size, density, viscosity, redispersibility, filling volume, uniformity of mass of delivered doses, dissolution rate, related substances, pH, microbiological purity and tightness of closure of the container.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 full-scale and 2 pilot-scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on 12 (3 full-scale and 9 pilot-scale) batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months), and one batch at 8°C (12 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in amber glass bottles (in upright and inverse position).
No significant changes were seen. Based on the data provided, a shelf life of 4 years without specific storage conditions was granted.
In-use stability data has been provided demonstrating that the product remains stable for 4 months following first opening of the bottle.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The drug substance UDCA is of ruminant animal origin. It is sourced from bovine bile. However, there is no risk of transmitting TSE as it meets the relevant criteria described in the current version of the Monograph of the European Pharmacopoeia.

II.2 Non-clinical aspects

This product is a line extension to Ursofalk capsules, which is available on the European market. No new preclinical data have been submitted. The MAH referred to the preclinical documentation included in the application for the immediate-release capsules. Therefore the application has not undergone additional preclinical assessment. This is acceptable for this type of application.
A non-clinical overview of the studies performed with regard to the pharmacology, pharmacokinetics and toxicology has been provided, which is based on non-clinical studies and supported by up-to-date and adequate scientific literature.

Environmental risk assessment
The product is intended as a substitute for other ursodeoxycholic acid containing products on the market. The approval of this product will not result in an increase in the total quantity of ursodeoxycholic acid

released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Ursodeoxycholic acid is a well-known active substance with established efficacy and tolerability.
An oral immediate-release dosage form is already available on the Dutch market: 250 mg capsules. The proposed formulation is an oral suspension containing 50 mg ursodeoxycholic acid/ml. The Board reckons that there is a need for an UDCA suspension, considering it can be swallowed more easily.

For the clinical data the MAH referred to the documentation included in the dossier of the Ursofalk capsules. Moreover, for this line extension, the MAH submitted a single and multiple dose study over 14 days with the 50 mg/ml suspension under fasting conditions.
The multiple dose arm is applied to assess and evaluate the biliary enrichment of ursodeoxycholic acid (UDCA) at the end of each treatment period (14 days), and to evaluate glyco-ursodeoxycholic acid and tauro-ursodeoxycholic acid in total biliary bile acids, and to evaluate the change in biliary bile acid composition (chenodeoxycholic acid, cholic acid, deoxycholic acid, lithocholic acid).

Bioequivalence study I
The study was conducted with Ursofalk 50 mg/ml suspension versus Ursofalk 250 mg capsules (from Germany). Doses of 750 mg were administered. The suspension was also compared to Ursodeoxycholic acid 150 and 300 mg capsules (from Italy). The data of this comparison are not considered relevant for this application, and are therefore not included in this report. The comparison to 250 mg capsules is representative for the Dutch market.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose and repeated dose, 2-way cross-over study was conducted in twenty-four healthy adult subjects, 11 females and 13 males, aged 21 - 55 years. Each subject received once daily a 750 mg dose of UDCA of both the test (suspension) and the 2 reference UDCA formulations (capsules) for 13 days. The capsules were administered in solid form with 150 ml water after an overnight fast; the suspension was taken with 135 ml of water. The first two doses of each treatment period were taken at the clinical facility, while the remaining daily doses were to be taken at home. For each subject there were 3 dosing periods, separated by a washout period of 14 days.

Blood samples were taken pre-dose and at 0.5, 1, 1.5, 2, 4, 8, 12 and 24 hours after administration of the products (only at day 1, single dose).
There were some critical findings in the GCP compliance in the conduct of the study and the validation of the analytical procedures.

Results
All 24 subjects completed the 3 study periods and were eligible for pharmacokinetic analysis.

The pharmacokinetic variables of UDCA are provided in the table below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of ursodeoxycholic acid under fed conditions.

Treatment N=24	**AUC_{0-12}** µmol.h/l	**AUC_{0-24}** µmol.h/l	**C_{max}** µmol.h/l	**t_{max}** h
Ursofalk suspension	150.52 ±1.05	251.55 ±75.89	22.65 ±1.07	3.56 ±0.47
Ursofalk 250	134.51	217.33	22.71	2.56

mg capsules	±1.05	±60.46	±1.07	±0.47
***Ratio (90% CI)**	1.12 (1.02-1.23)	1.14 (1.03-1.27)	1.01 (0.84-1.21)	-
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration (0-12 hour) **t_{max}** time for maximum concentration (0-12 hour)				

The MAH considers AUC_{0-12h} the pivotal variable (and for which bioequivalence could be proven) as indicated that due to enterohepatic recirculation of the bile acids AUC_{0-24h} may be not reliable. This is however difficult to separate from a certain time point. Moreover, the protocol stated that AUC_{0-24h} would be assessed as primary variable. As requested by the MEB, the MAH also provided data on AUC_{0-}24h which were just outside the normal acceptable CI intervals.

Therefore no bioequivalence within the acceptance criteria of 0.80-1.25 could be obtained for AUC_{0-24h}. However, the MEB accepted the justification of the critical findings from the MAH.

The second study part, evaluation of duodenal bile acids is considered not pivotal, and not informative for this bioequivalence study. Moreover, the analytical evaluation of the study had limitations and the number of subjects finalising the study is too limited, which made the analysis inconclusive.

On request of the MEB the MAH submitted the results of a second bioequivalence study.

Bioequivalence study II

This was a randomized crossover design study to evaluate the bioequivalence of two different orally administered preparations of ursodeoxycholic acid (UDCA) under both fed and fasting conditions by assessing as the primary end-point the plasma UDCA concentrations and pharmacokinetics for Cmin, Tmax, Cmax and AUCTau, following multiple oral doses. The test product was Ursofalk 50 mg/ml suspension, the reference product Urso 250 mg tablets (US market). There was no wash-out period.

Thirty-six (36) healthy adult volunteers (29 males/7 females, aged 18-49 years) were included to receive two multiple oral dose regimens (250 mg) of ursodeoxycholic acid initially under fed conditions followed by fasting conditions without a washout period. All doses on days 1-4 and days 7-10 were administered under fed conditions. Doses on days 5 and 6 and days 11 and 12 were administered under fasting conditions one (1) hour prior breakfast or dinner. The subjects were administered meals which contained 1000 calories with 30% of those calories from fat. Doses were administered during 12 days.

Four subjects were withdrawn due to AEs or withdrew for personal reasons.

Table 2. ANOVA – Two-Tail T-test(90% C.I results) UDCA fed state: Treatment B (suspension) versus Treatment A (tablet).

Parameter	Pair	Reference (A)	Test	Difference Test-Reference	Ratio Test/Reference	(90% Conf Int)
$AUC_{(0-Tau)}$	A-B	14865.98	14321.49	-544.4921	0.963	(0.898, 1.034)
C_{max}	A-B	3317.33	2836.33	-481.0081	0.855	(0.795, 0.919)
C_{min}	A-B	653.45	690.10	36.65	1.056	(0.949, 1.175)

Table 3. ANOVA – Two-Tail T-test(90% C.I results) UDCA fasting state: Treatment B (suspension) versus Treatment A (tablet).

Parameter	Pair	Reference (A)	Test	Difference Test-Reference	Ratio Test/Reference	(90% Conf Int)
$AUC_{(0\text{-}Tau)}$	A-B	12921.96	12803.65	-118.31	0.991	(0.914, 1.075)
C_{max}	A-B	3088.21	3071.46	-16.75	0.995	(0.932, 1.062)
C_{min}	A-B	632.93	617.77	-15.16	0.976	(0.853, 1.117)

The bioequivalence study submitted was intended for obtaining a marketing authorisation in the United States. As such, a FDA drug product has been used (Urso 250 mg tablets) as a reference. This application concerns a national procedure for which the comparison to Urso 250 mg tablets is not relevant. The only conclusion that can be drawn is that after administration of the suspension, the availability of the active substance is comparable to different ursodeoxycholic acid containing products.

Conclusion on clinical aspects

The Board recognises that there is a need for an UDCA suspension, considering it can be swallowed more easily.

The following was noted:

- Considering the submitted data, it can be concluded that UDCA absorption is comparable to different products.
- The excipients in the Ursofalk capsule (maize starch, silica, magnesium stearate) and in the suspension (benzoic acid, purified water, xylitol, glycerol, microcristalline cellulose carmellose sodium, propylene glycol, sodium citrate, sodium cyclamate, citric acid, sodium chloride, lemon flavouring) are not considered to affect bioavailability.
- In addition, comparable bioavailability is shown to the US product Urso 250 mg tablets, which contains the more critical excipient sodium lauryl sulphate.
- UDCA is a bile acid which effects a reduction in cholesterol in biliary fluid primarily by dispersing the cholesterol and forming a liquid-crystal phase. After oral administration, UDCA (an endogenous compound) is absorbed and efficiently extracted by the liver and excreted in the bile as glycine and taurine conjugates. UDCA is only absorbed systemically to a small extent, and this portion does not exhibit systemic action.

Considering these points, no major issues with respect to bioavailability are expected between Ursofalk capsules and suspension. As UDCA is acting in the bile and as UDCA is extracted by the liver after absorption before reaching the systemic circulation, it can be questioned to which extent systemic concentrations are predictive for the effect. The benefit/risk of the suspension vs. the capsule is considered comparable. Based on this the Ursofalk suspension is considered approvable from a clinical point of view.

Risk management plan

The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks. The safety profile of Ursofalk suspension is expected to be similar to that of Ursofalk capsules. No additional risk management activities are considered necessary.

Product information

SmPC

The content of the SmPC approved during the national procedure is in accordance with that accepted for Ursofalk capsules.

Readability test

The package leaflet has not been evaluated via a user consultation study. Reference is made to the successfully user tested PL for Ursofalk capsules. The PL for the suspension has been revised in accordance with the user testing result of the capsules' PL. A detailed bridging report has been provided. It is agreed that separate user testing is not required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ursofalk 50 mg/ml suspension has a proven chemical-pharmaceutical quality and is an approvable line extension to Ursofalk 250 mg capsules. Ursofalk capsules is a well-known medicinal product with an established favourable efficacy and safety profile.

UDCA is a substance that acts in the bile and is extracted by the liver after absorption before reaching the systemic circulation. It is therefore questioned to which extent systemic concentrations are predictive for the effect. Although bioequivalence with the capsule formulation has not been demonstrated, no major issues with respect to bioavailability are expected between Ursofalk capsules and suspension.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC is consistent with that of Ursofalk capsules. The SmPC, package leaflet and labelling are in the agreed templates.

The Board discussed the clinical documentation for this application on several occasions in 2008, 2009 and 2012. The conclusion was that, considering the local action of the product, the clinical results sufficiently support this line extension.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Ursofalk 50 mg/ml suspension was authorised in the Netherlands on 18 December 2012.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
UDCA	Ursodeoxycholic Acid
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Update of the quality dossier.	--	II/G	19-3-2013	28-6-2013	Approval	N