

**PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands**

**Ursofalk 500 mg film-coated tablets
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 112405

17 April 2014

Pharmacotherapeutic group:	bile acid preparations
ATC code:	A05AA02
Route of administration:	oral
Therapeutic indication:	dissolution of cholesterol gallstones; primary 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:	16 May 2013
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 500 mg film-coated tablets from Dr. Falk Pharma Benelux B.V. The date of authorisation was on 16 May 2013 in the Netherlands.

The product is indicated for:

- dissolution of cholesterol gallstones in patients
 - with one or more radiolucent (i.e. non-radio opaque) cholesterol gallstones, preferably less than 2 cm in diameter, in a well functioning gallbladder
 - who refuse surgical intervention or in whom surgical intervention is not indicated
 - in whom super saturation of cholesterol has been demonstrated in chemical analysis of bile samples obtained by duodenal drainage
- adjuvant medication before and after 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: a film-coated tablet with a higher strength in addition to the previously authorised capsules. Ursofalk® 500 mg film-coated tablets have been developed to provide a single-unit UDCA formulation with a high content of the active ingredient to reduce the need for intake of numerous units, which in turn should improve patients' compliance to this therapy, which is always intended for long-term and, in many cases, even life-long treatment.

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 the results of three bioequivalence studies with Ursofalk 500 mg tablets versus the Ursofalk 250 mg capsules, a pharmacokinetic study to investigate biliary enrichment with single daily doses and a randomised, double-blind crossover clinical trial in PBC patients comparing the efficacy of the treatment with Ursofalk 500 mg film-coated tablets to that of Ursofalk 250 mg capsules. 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. No polymorphism is known for UDCA.

The CEP procedure is used for the three 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 European Pharmacopoeia.

Manufacturing process

CEPs have 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 Ph.Eur. monograph on ursodeoxycholic acid and the tests stated on the individual CEPs with an additional test and requirement for particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches of drug substance from each supplier.

Stability of drug substance

For the first CEP holder, stability data on the active substance have been provided for 9 full-scale batches stored at 25°C/60% RH (36-60 months) and six full-scaled batches stored at 40°C/75% RH (6 months). No changes or trends were observed in any of the tested parameters. The proposed retest period of 5 years at room temperature was granted.

For the second manufacturer, stability data on the active substance have been provided for three full-scale batches stored at 25°C/60% RH (12 months) and three pilot-scale batches stored at 40°C/75% RH (6 months). No changes or trends were seen in any of the tested parameters at both storage conditions. Based on these data the proposed retest period of 12 months without any special storage requirements is justified.

For the active substance from the third CEP holder no data were provided. The applicable retest period of the substance is 60 months 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 500 mg is a white, oblong film-coated tablet with a double-sided breaking notch containing 500 mg of ursodeoxycholic acid. The tablets can be divided into equal halves.

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

The excipients are: cellulose microcrystalline, povidone K25, crospovidone type A, talcum, magnesium stearate, colloidal anhydrous silica and polysorbate 80. The tablet coating consists of hypromellose, talc and macrogol 6000.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies focussed on the use of the coating to mask the bitter taste of the product and further on the development of an in-house dissolution test. The suitability of the breaking notch was adequately demonstrated with the Ph.Eur. test on equal divisibility. The batches used in the clinical studies were manufactured according to the finalized manufacturing formula and process. Certificates of analysis on the test and reference batches used in the bioequivalence studies have been provided, confirming that the assayed content is comparable. Similarity in dissolution was demonstrated in pH 7.5 medium between the test and reference batches used in the studies. The absence of comparative dissolution studies in media of lower pH was sufficiently justified based on solubility characteristics of the drug substance. The development of the product has been described in sufficient detail.

Manufacturing process

The manufacturing process is a standard process and mainly consists of wet granulation, compression, film-coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for two pilot-scale and three full-scale batches.

Control of excipients

The excipients comply with the Ph.Eur. The specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, disintegration time, uniformity of dosage units, residual solvents, identity, assay, dissolution, purity and microbiological quality. The release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided five pilot-scale and ten full-scale batches stored at 25°C/60% RH (12-60 months; 12 batches), 30°C/35% RH (12 months; 1 batch), 30°C/65% RH (60 months; 1 batch), 30°C/75% RH (3-12 months; 4 batches) and 40°C/75% RH (6 months; 7 batches). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC//Al blisters. No changes or trends are seen in any of the tested parameters at all tested storage conditions. The drug product was demonstrated to be photostable. The proposed shelf-life of 4 years without any special storage requirements was therefore granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The active substance ursodeoxycholic as well as the stearic acid used for the manufacture of the excipient magnesium stearate are of animal origin susceptible to TSE. CEPs have been provided for ursodeoxycholic acid as well as for stearic acid confirming compliance with the current version of the monograph 'Products with risk of transmitting agents of animal spongiform encephalopathies of the Ph.Eur.'

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 a film-coated tablet containing 500 mg ursodeoxycholic acid.

Ursofalk 500 mg film-coated tablets have been developed to provide a single-unit UDCA formulation with a high content of the active ingredient to reduce the need for intake of numerous units, which in turn may improve patients' compliance to this therapy, which is always intended for long-term and, in many cases, even life-long treatment. The Board considers this rationale for the development of a higher strength tablet appropriate.

Pharmacokinetics

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 bioequivalence studies in which the pharmacokinetic profile of the 500 mg tablet was compared with the Ursofalk 250 mg capsule. In addition, the availability of UDCA in the bile was assessed.

Conventional bioequivalence studies were performed as required in accordance with the "Guideline on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/1401/98)". At the time of the planning of the first study (URT-10/BIO), no reliable data were available to perform a valid sample size calculation. Based on an erroneously low estimated variability of the plasma concentrations of UDCA, URT-10/BIO was significantly underpowered and thus could not yield valid results.

Results of a second, adequately powered study (URT-12/BIO) showed that the conditions of bioequivalence of Ursofalk® 500 mg film-coated tablets and an established UDCA preparation based on plasma concentrations were met. An additional confirmatory bioequivalence study, study URT-13/BIO was performed. In this study, bioequivalence was confirmed again with regard to AUC. The relevance of bioavailability and bioequivalence assessment based on plasma concentrations of UDCA evaluated after single doses and at single time points is questionable. It is unsure whether efficacy of UDCA in gallstone disease and PBC can be established in this way. With these considerations in mind, study URT-14/BIO is presented and discussed below as the pivotal study on bioavailability, as it is the only study that directly assesses the availability of UDCA in the bile, *i.e.* in a compartment of the enterohepatic circulation.

Summary of the bioequivalence studies URT-10/BIO, URT-12/BIO and URT-13/BIO

The three clinical pharmacology studies were single center, single dose, controlled, randomised, cross-over bioequivalence studies conducted in healthy volunteers. In total 72 healthy female and male volunteers completed the Ursofalk bioequivalence studies in which they received 500 mg Ursofalk tablets or two 250 mg Ursofalk capsules with a wash-out period of 14 days. One subject dropped out due to an adverse event. The formulations were administered with 200 ml of water in a fasting state after which blood samples were taken up to 12 hours post-dosing for pharmacokinetic analysis. Overall these studies proved bioequivalence for AUC between the 250 mg capsule and 500 mg tablet formulations. For C_{max} the 90% CI were outside the normal acceptance criteria (80-125%), however for one trial in the protocol the pre-set limits for C_{max} were 73-143% based on which it was concluded that this criterion was fulfilled in that particular trial only.

Pivotal Study URT-14/BIO

Aim of this open-label, non-randomised pharmacokinetic study was to show that UDCA in single daily doses results in an adequate biliary enrichment. The study investigated dosages within the proposed dose range of 14 ± 2 mg/kg bw given as a single daily dose.

In this study, 11 PBC patients and 11 healthy subjects were treated with Ursofalk® 500 mg tablets at a dose of 15 mg/kg bw in a single daily dose for 3 weeks. Biliary enrichment (sampled by endoscopy after contraction of gall bladder) and plasma pharmacokinetics were measured. The results are shown below:

Table 1: UDCA plasma pharmacokinetics and percentage of UDCA + UDCA metabolites based on total bile acids + metabolites in cystic bile (“biliary UDCA enrichment”) in PBC patients and healthy volunteers treated with Ursofalk 500 mg tablets once daily for 3 weeks (mean \pm SD)

Parameters	PBC patients (n=11)	Healthy volunteers (n=11)
Mean UDCA dose during the trial (mg/kg bw/day)	14.23 \pm 1.45	14.20 \pm 0.96
Plasma pharmacokinetics		
AUC _{0-24h} (μ mol x h/l)	53.10 \pm 14.45	49.83 \pm 19.00
C _{max} (μ mol/l)	15.45 \pm 7.60	15.19 \pm 7.62
t _{max} (h)	2.23 \pm 0.87	2.47 \pm 0.69
Biliary UDCA enrichment (%)		
Day 1 (Baseline)	0.88 \pm 0.91	1.51 \pm 1.59
Day 23	42.83 \pm 10.48	39.72 \pm 9.55

Treatment with Ursofalk® tablets in a single daily dose of 15 mg/kg bw led to biliary enrichment of UDCA and metabolites (UDCA-gluc, Tau-UDCA, Gly-UDCA, Iso-UDCA, UDCA sulfate) of about 40% in both PBC and in healthy volunteers, which is in the same range as previously found for Ursofalk® capsules. A weak correlation was found between the concentration of UDCA and metabolites in cystic bile with AUC (0-24h) of UDCA in plasma ($r=0.434$, $p=0.0435$), but there was no correlation with C_{max} ($r=0.051$, $p=0.8204$). As concluded for Ursofalk capsules (NL License RVG 08384) the data from literature and the studies performed by the MAH indicated that single daily dosing and multiple daily dosing are unlikely to differ significantly in efficacy. Plasma concentrations at single isolated time points such as peak plasma concentrations are considered not relevant in this regard.

A post-hoc analysis of serum liver parameters was performed on 5 PBC patients who had been on pre-trial treatment with Ursofalk® capsules. The results showed that serum concentrations of markers of early cholestasis and of hepatocellular damage reached similar levels after 3 weeks of treatment with Ursofalk tablets in a single daily dose as compared to the end of the pre-trial treatment with Ursofalk® capsules. It is concluded that treatment with Ursofalk® tablets in a daily dose of 15 mg/kg bw given as a single daily dose led to biliary enrichment and clinical efficacy.

Clinical efficacy and safety

Pivotal study URT-15/PBC

This was a double-blind, double-dummy, randomised, cross-over, multicenter clinical trial to prove efficacy and safety of Ursofalk 500 mg tablets compared to Ursofalk 250 mg capsules. Sixty-five (65) patients received treatment with one of the two formulations (14 ± 2 mg/kg body weight (bw) /d), during 12 weeks followed by the alternative formulation for 12 weeks. All patients had primary biliary cirrhosis (PBC) in early stages and were UDCA responders (normalisation of AP or reduction of AP \geq 40% after onset of UDCA).

The primary efficacy endpoint used was the relative differences of AP (alkaline phosphatase), GGT (γ -glutamyl transferase) and ALT (alanine aminotransferase) between the end of the treatment-period with Ursafalk 250 mg capsules and the end of the treatment-period with Ursafalk 500 mg tablets.

No difference could be demonstrated between Ursafalk 500 mg tablets compared to Ursafalk 250 mg capsules in controlling the liver enzymes AP, GGT and ALT in patients with PBC. Results of the secondary efficacy endpoints support the conclusion.

The relative differences in liver enzymes values were large, in particular for ALT. However, the absolute differences in liver enzymes were small supporting that there are no clinically relevant differences between the formulations.

The safety results reveal no new findings and demonstrate a comparable safety profile for Ursafalk tablets and capsules.

In conclusion, Study URT-15/PBC shows that a 12 week treatment with Ursafalk 500 mg tablets was therapeutically non-inferior to a 12 week treatment with Ursafalk 250 mg capsules in controlling liver enzyme values of AP, GGT and ALT in patients with PBC. The subgroup analyses and secondary efficacy endpoints are supportive of this finding.

Overall conclusion

The data submitted showed that the Ursafalk 500 mg tablet is bioequivalent to Ursafalk 250 mg capsules with regard to AUC. For C_{max} no bioequivalence could be shown, C_{max} values were lower. However, administration of the 500 mg tablet in the therapeutic dose of 15 mg/kg bw as a single daily dose led to biliary enrichment of 40% which is generally considered to be associated with clinical efficacy in the treatment of cholesterol gallstones and PBC. A weak correlation was found between the concentration of UDCA and metabolites in cystic bile with AUC (0-24h) of UDCA in plasma, but no correlation was found for C_{max} . This indicates that lower C_{max} values does not affect efficacy.

This was also proven in the clinical efficacy and safety study URT-15/PBC where no difference between Ursafalk tablets and Ursafalk capsules could be shown in PBC patients.

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 Ursafalk tablets is expected to be similar to that of Ursafalk 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 Ursafalk 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 Ursafalk capsules. The PL for the tablets 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 500 mg film-coated tablets 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 been demonstrated for AUC only and not for C_{max} , no major issues with respect to bioavailability are expected between Ursofalk capsules and tablets. Moreover, the MAH has shown that administration of the 500 mg tablet in the therapeutic dose of 15 mg/kg bw as a single daily dose leads to biliary enrichment of 40%.

Additionally, a pivotal clinical study showed no difference between Ursofalk 500 mg tablets and Ursofalk 250 mg capsules in controlling the liver enzymes AP, GGT and ALT in patients with PBC.

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 MEB, on the basis of the data submitted, considered that Ursofalk 500 mg demonstrated a satisfactory risk/benefit profile and therefore granted a marketing authorisation. Ursofalk 500 mg film-coated tablets was authorised in the Netherlands on 16 May 2013.

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
PBC	Primary Biliary Cirrhosis
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
t _{1/2}	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