

## IPAR



### **PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE**

Scientific discussion

Ursofalk 250 Milligram Oral Suspension

URSODEOXYCHOLIC ACID

PA 573/5/2

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the IMB for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the IMB leading to the approval of the medicinal product for marketing in Ireland.

## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Ursofalk 250mg suspension, from Dr. Falk Pharma GmbH, Germany on 14<sup>th</sup> January 2011 for the dissolution of gall stones.

The application for Ursofalk Suspension was submitted as a new national application as a so called line extension to the existing authorisation for Ursofalk 250mg Capsules.

The product is available on a prescription only basis.  
The indications for both products are the same.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at <http://www.imb.ie/>

Name of the product	Ursofalk 250 Milligram Oral Suspension
Name(s) of the active substance(s) (INN)	URSODEOXYCHOLIC ACID
Pharmacotherapeutic classification (ATC code)	AO5AA, A05B
Pharmaceutical form and strength(s)	Suspension 250mg/5ml
Marketing Authorisation Number(s) in Ireland (PA)	PA 573/5/2
Marketing Authorisation Holder	Dr. Falk Pharma GmbH, Germany

## II QUALITY ASPECTS

### II.1. Introduction

This application is for Ursofalk 250mg Suspension

### II.2 Drug substance

The active substance is ursodeoxycholic acid an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality as it meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

### II.3 Medicinal product

#### P.1 Composition

Brief description of the dosage form

<b>Name of active substance</b>	<b>Quantity</b>	<b>Unit</b>
Ursodeoxycholic acid	250.00	mg

#### **Name of excipients**

Benzoic acid  
Water, purified  
Xylitol  
Glycerol

Avicel RC-591, consisting of:  
Cellulose microcrystalline  
Carboxymethylcellulose sodium  
Propylene glycol  
Sodium citrate  
Sodium cyclamate  
Citric acid, anhydrous  
Sodium chloride  
Lemon flavouring  
(Givaudan PHL-134488)

## P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

## P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to ICH guidelines and the process is thus considered to be sufficiently validated.

## P.4 Control of Other Substances Excipients

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

## P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for a suspension, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

## P.6 Packaging material

The product is presented in brown glass bottles with a child resistant cap.

Evidence has been provided that the glass complies with Ph. Eur. requirements.

## P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 4years when stored at no special storage conditions.

Following the opening of the container the product has an in-use stability period of 4 months after which it must be discarded.

## II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and

pharmaceutical documentation has been provided, assuring consistent quality of Ursofalk 250mg suspension.

### **III NON-CLINICAL ASPECTS**

#### **III.1 Introduction**

This active substance has been available on the European market since 1979. Preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

### **IV CLINICAL ASPECTS**

#### **IV.1 Introduction**

Ursodeoxycholic acid is a well known active substance with established efficacy and tolerability used in the dissolution of cholesterol gallstones and also in the treatment of primary biliary cirrhosis of the liver.

The content of the SPC approved during the national procedure is in accordance with that accepted for the existing authorised formulation, Ursofalk 250 mg capsules (PA 573/5/1) marketed by Dr. Falk Pharma UK Ltd.

The new formulation in suspension had been developed to offer an alternative liquid dosage form to patients who have difficulty in swallowing solid dosage forms.

A single dose study in healthy volunteers was conducted to compare the Bioavailability of Ursofalk suspension and the reference products Ursofalk capsules.

The study followed a balanced randomised three-way cross-over design with the following formulations:

- Ursofalk 250 mg capsules (Falk, Germany)
- Ursofalk 150/300 mg capsules (Knoll BASF Pharma, Italy)
- Ursofalk suspension.

Each subject received 750 mg UDCA daily orally (equivalent to 10-15 mg/kg body weight/day) in a single bolus dose as either suspension or as capsules after a 14-day washout period to ensure that plasma and biliary UDCA levels returned to baseline values.

The mean peak plasma concentration (C<sub>max</sub>) and bioavailability as measured from the AUC<sub>0-24h</sub> after single administration of 750 mg UDCA as Ursofalk suspension and Ursofalk capsules 250 mg respectively, were comparable. The 90% confidence interval for the ratio of geometric means for C<sub>max</sub> and AUC<sub>0-24h</sub> was between 0.8 and 1.25, the range of predetermined bioequivalence.

#### **IV.5 Clinical Safety**

Ursodeoxycholic acid has been in therapeutic use for over 20 years; its safety profile is well established and adequately described in the product information.

#### **IV.6 Discussion on the clinical aspects**

Please see below.

### **V OVERALL CONCLUSIONS**

#### **BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

Ursofalk suspension 250 mg/5mL is a so called line extension of Ursofalk 250 mg Capsules which contain ursodeoxycholic acid, a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SPC is consistent with that of the already approved pharmaceutical form.

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

The IMB, on the basis of the data submitted considered that Ursosalk suspension 250 mg/5mL demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.