

Public Assessment Report

Scientific discussion

Ursodeoxycholic acid Orion **(ursodeoxycholic acid)**

SE/H/1656/01/DC

This module reflects the scientific discussion for the approval of Ursodeoxycholic acid Orion. The procedure was finalised on 2017-08-16. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

The application for Ursodeoxycholic acid Orion, 250 mg, capsule, hard, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Orion Corporation applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Ursofalk, 250 mg, capsule, hard authorised in DE since 1999, with Dr. Falk Pharma GmbH as marketing authorisation holder.

The reference product used in the bioequivalence study is Ursofalk, 250 mg, capsule, hard from DE with Dr. Falk Pharma GmbH as marketing authorisation holder.

Similarity to medicinal products with orphan drug status

According to Article 8.1 of Regulation (EC) No 141/2000, where a marketing authorization in respect of an orphan medicinal product is granted, the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorization, or grant a marketing authorisation, accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product (so-called 10 year market exclusivity).

The Applicant has completed module 1.7.1 (similarity) and claims that Ursodeoxycholic acid Orion is not similar to OCALIVA (obeticholic acid). The claim of non similarity is based on the comparison with the molecular structural features, mechanism of action and therapeutic indications, as defined in the Article 3 of Regulatory (EC) No 847/2000.

The RMS agrees with the Applicant that the molecular structures are similar as such, while the overall conclusion is that Ursodeoxycholic acid Orion is not similar to OCALIVA (obeticholic acid).

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Bioequivalence was evaluated in one single-dose, three-way crossover study conducted in 54 healthy volunteers, comparing ursodeoxycholic acid, 250 mg, hard capsule with Ursfolk, 250 mg, hard capsule under fasting conditions. The study was conducted at CEPHA s.r.o., Czech Republic between 17th August and 7th October 2015. Blood samples were collected pre-dose and up to 72 hours post-dose. The study design is considered acceptable. Plasma concentrations of ursodeoxycholic acid (UDCA), tauroursodeoxycholic acid (TUDCA) and glyoursodeoxycholic acid (GUDCA) were determined with an adequately validated LC-MS/MS method.

For AUC_{0-t} and C_{max} for baseline-corrected free UDCA (primary variables) the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%, see Table 1.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, t_{max} median, range) for baseline corrected free UDCA, n=50.

Treatment	AUC _{0-t} ng*h/ml	AUC _{0-12h} ng*h/ml	C _{max} ng/ml	t _{max} h
Test	54765.7 $\pm$ 18932.9	25804.0 $\pm$ 6299.4	8963.9 $\pm$ 3199.8	2.25 (0.50, 6.00)
Reference 2	58974.8 $\pm$ 25022.5	27307.5 $\pm$ 8262.4	10526.0 $\pm$ 5115.2	2.00 (0.50, 6.00)
*Ratio (90% CI)	0.9503 0.8841 – 1.0215	0.9591 0.9107-1.0100	0.8887 0.8197 – 0.9635	-
	AUC _{0-t} area under the plasma concentration-time curve from time zero to t hours C _{max} maximum plasma concentration t _{max} time for maximum plasma concentration			

*calculated based on ln-transformed data

Based on the submitted bioequivalence study, Ursodeoxycholic acid Orion is considered bioequivalent with Ursofalk.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

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 Ursodeoxycholic acid Orion.

Safety specification

Summary of safety concerns	
Important identified risks	• Diarrhoea • Use in patients with acute inflammation of the gall bladder or the biliary tract, occlusion of the biliary tract, frequent episodes of biliary colic, radio-opaque calcified gallstones or impaired contractility of the gall bladder • Use in children with biliary atresia following unsuccessful portoenterostomy or without recovery of good bile flow
Important potential risks	• Decompensation of hepatic cirrhosis in patients with late stage primary biliary cirrhosis • Use during pregnancy
Missing information	• Use during lactation • Effects on fertility

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of Safety Concerns and Planned Risk Minimisation Activities as proposed/ approved in RMP

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: • Diarrhoea	Information given in SmPC sections 4.4, 4.8 and 4.9. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.
Important identified risks: • Use in patients with acute inflammation of the gall bladder or the biliary tract, occlusion of the biliary tract, frequent episodes of biliary colic, radio-opaque calcified gallstones or impaired contractility of the gall bladder	Information given in SmPC sections 4.1, 4.2, 4.3, 4.4 and 4.8. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks: • Use in children with biliary atresia following unsuccessful portoenterostomy or without recovery of good bile flow	Information given in SmPC section 4.3. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.
Important potential risks: • Decompensation of hepatic cirrhosis in patients with late stage primary biliary cirrhosis	Information given in SmPC sections 4.4 and 4.8. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.
Important potential risks: • Use during pregnancy	Information given in SmPC sections 4.6 and 5.3. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.
Missing information: • Use during lactation	Information given in SmPC section 4.6. Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	None proposed.
Missing information: • Effects on fertility	Information given in SmPC sections 4.6 and 5.3.	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Other routine risk minimisation measures: • Prescription only medicine • Close monitoring through routine pharmacovigilance	

Summary of the RMP

The RMP is approved

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Ursotalk, 111:2009/28228 and Venlafaxin Orion, DE/H/1420/01-03/DC. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Ursodeoxycholic acid Orion, is found adequate. There are no objections to approval of Ursodeoxycholic acid Orion, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.

The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The Decentralised procedure for Ursodeoxycholic acid Orion, 250 mg, capsule, hard was positively finalised on 2017-08-16.

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/non approval	Summary/Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)