COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ursodeoxycholzuur Glenmark 150 mg, 300 mg, and 450 mg tablets

(ursodeoxycholic acid)

NL/H/4010/001-003/DC

Date: 20 November 2018

This module reflects the scientific discussion for the approval of Ursodeoxycholzuur Glenmark 150 mg, 300 mg, and 450 mg tablets. The procedure was finalised at 25 April 2018. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ursodeoxycholzuur Glenmark 150 mg, 300 mg, and 450 mg tablets from Glenmark Pharmaceuticals Europe Ltd.

The product is indicated for the treatment of:

- The dissolution of cholesterol stones in patients:
  - who have one or more X-ray translucent (X-ray negative) gallstones, preferably with a diameter of not more than 2 cm, in a well-functioning gall bladder;
  - who refuse a surgical intervention or where surgery is not indicated;
  - in whom an oversaturation of cholesterol has been shown by chemical analysis of the bile produced by duodenum sondage.
- Primary Biliary Cholangitis (PBC)

Paediatric population
Hepatobiliary disorders in children with cystic fibrosis aged 6 to 18 years.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Ursochol 150 mg, 300 mg, and 450 mg capsules, hard (NL License RVG 07718, 09307, 29828) which have been registered in The Netherlands by Zambon BV since respectively 7 February 1979, 6 May 1982, and 4 April 2005.

The concerned member states (CMS) involved in this procedure were Spain and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

Similarity assessment in view of the orphan drug legislation
The MAH provided a similarity assessment report versus the orphan medicinal product Ocaliva (obeticholic acid). Obeticholic acid received its orphan designation on 27 July 2010 (EU/3/10/753) for the treatment of PBC and the European Commission granted a marketing authorisation valid throughout the European Union for Ocaliva on 12 December 2016.
It is concluded that, having considered the arguments presented by the MAH of ursodeoxycholic acid, the indication and mechanism of action of ursodeoxycholic acid and obeticholic acid are not similar in the context of orphan medicinal products.

II. QUALITY ASPECTS

II.1 Introduction

Ursodeoxycholzuur Glenmark is a tablet in three strengths.

- 150 mg: White to off-white, round shaped uncoated tablets with break line and ´G´ ´442´ engraved on one side and plain on the other side.
- 300 mg: White to off-white, round shaped uncoated tablets with break line and ´G´ ´443´ engraved on one side and plain on the other side.
- 450 mg: White to off-white, capsule shaped uncoated tablets with break line and ´G´ ´445´ engraved on one side and plain on the other side.

Each tablet contains 150 mg, 300 mg or 450 mg of ursodeoxycholic acid (UDCA).

The tablet is packed in clear PVC/PVDC – plain aluminium foil.

The excipients are cellulose microcrystalline (microcel 101) (E460), polyvinyl pyrrolidone (plasdone K-90) (E1201), magnesium stearate (E572) and sodium starch glycolate type A (primojel).

The composition of the strengths is quantitatively proportional.

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, freely soluble in ethanol (96%), slightly soluble in acetone and practically insoluble in methylene chloride, slightly, etc. soluble in water. Furthermore the drug substance is considered to be a BCS class II compound.

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. It is in line with the CEP, and includes additional requirements for microbial enumeration, specified microorganisms and particle size.
Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance
Stability data on the active substance have been provided for 42 full scaled batches stored at 25°C/60% RH (up to 60 months) and 40°C/75% RH (6 months). The batches were stored in the proposed packaging.
No trends or out of specification results are observed at accelerated and long term conditions in any of the tested batches. Based on the data submitted a retest period could be granted of five years without special storage conditions.

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 explained. Based on the clinical and pharmacokinetic characteristics as well as the *in vitro* dissolution and physicochemical characteristics of the reference product, a quality target product profile (QTPP) was defined. Based on the QTPP, product understanding, reference product characterisation and previous experience gained from developed immediate release tablets, quality attributes are identified and an initial risk assessment of formulation component attributes was performed.

A bioequivalence study was submitted to demonstrate bioequivalence between Ursodeoxycholzuur Glenmark 450 mg and the reference medicinal product, Urschel 450 mg. The test batch used in the bioequivalence study was manufactured according to the finalised manufacturing process and composition. Comparative *in vitro* dissolution profiles between the bioequivalence batch and reference batch are generated.
Comparative dissolution profiles and similarity between the strengths are demonstrated in physiological pH media fulfilling the biowaiver criteria.

Manufacturing process
The manufacturing process is a wet granulation process followed by compression into tablets. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full scaled batches per strength in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. 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, identity, average weight, dissolution, uniformity of dosage units, assay, water content, related substances and microbiological enumeration tests and tests for specified microorganisms. The release and shelf-life requirements/limits are identical with exception of the water content limits. 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 full scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided on three full scaled batches per strength stored at 25°C/60% RH (18 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC-Al blister pack. Out of specification results for dissolution were observed in the batches stored at intermediate conditions after 12 months of storage. No other trends were observed.
Based on the provided stability data the proposed shelf life of 18 months with storage condition as 'do not store above 25°C' in clear PVC/PVDC – plain aluminium foil blisters is acceptable.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ursodeoxycholzuur Glenmark 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 Ursodeoxycholzuur Glenmark is intended for generic 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 generic formulation of Ursochol 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 generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ursodeoxycholzuur Glenmark 450 mg tablets (Glenmark Pharmaceuticals Europe Ltd) is compared with the pharmacokinetic profile of the reference product Ursochol 450 mg tablets (Zambon GmbH, The Netherlands).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

<u>Biowaiver</u>
For the lower strengths a biowaiver is accepted:

- The tablets are quantitatively proportional.
- The tablets are manufactured by the same manufacturer and manufacturing process.
- Comparative dissolution is shown between the different strengths.

Bioequivalence studies

Design

A single-dose, two-way, two-period, randomised, crossover bioequivalence study was carried out under fed conditions in 48 healthy male subjects, aged 22-44 years. Each subject received a single dose (450 mg) of one of the two ursodeoxycholic acid formulations. Unconjugated ursodeoxycholic acid is considered the pivotal analyte for bioequivalence assessment. Total ursodeoxycholic acid data is only considered supportive. The tablet was orally administered with 240 ml water after intake of a high caloric, high fat breakfast. There were two dosing periods, separated by a washout period of 29 days.

Blood samples were collected -48, -36, -30, -24, -18, -12, -6, and 0 hours pre-dose administrations and at 0.16, 0.33, 0.67, 1.0, 1.33, 1.67, 2.00, 2.33, 2.67, 3.0, 3.5, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0, 60.0 and 72.0 after administration of the products.

The design of the study is acceptable. A single dose, crossover study to assess bioequivalence is considered adequate. According to the SmPC, the tablets should be taken after a meal. As such, the fed condition applied in the study is considered adequate.
Pre-dose sampling was needed in order to determine baseline plasma concentrations of endogenous ursodeoxycholic acid and adjustment of post dose concentration was performed by standard subtractive method.
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. A washout period of at least 29 days is applied, and based upon the observed half-life of ursodeoxycholic acid in this study (about 1 day), this is acceptable. Ursodeoxycholic acid 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 hours is not considered necessary for any immediate release formulation irrespective of the half life of the drug.

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

One subject withdrew during period I for personal reasons. Therefore 47 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ursodeoxycholic acid under fed conditions.

Treatment N=47	AUC_{0-t} (ng.h/ml)	$AUC_{0-\infty}$ (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)
Non baseline corrected					
Test	29141 ± 10271	33378 ± 12207	5639 ± 2370	2.0 (1.0 - 5.0)	22 ± 25
Reference	30049 ± 10755	34986 ± 13621	6032 ± 2505	2.0 (1.0 - 5.0)	20 ± 9
***Ratio (90% CI)**	0.98 (0.93 - 1.04)	--	0.94 (0.85 - 1.03)	--	--
CV (%)	16	--	27.7	--	--
Baseline corrected					
Test	27642 ± 8976	35763 ± 34211	5618 ± 2374	2.0 (1.0 -5.0)	23 ± 30
Reference	28503 ± 9296	33188 ± 12979	6012 ± 2503	2.0 (1.0 - 5.0)	19 ± 9
***Ratio (90% CI)**	0.98 (0.93 - 1.03)	--	0.94 (0.85 - 1.03)	--	--
CV (%)	16.1	--	27.9	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life
CV coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of baseline corrected unconjugated UDCA the test product is considered bioequivalent with the reference product. The supportive non baseline corrected unconjugated UDCA data showed also bioequivalence.

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 Ursodeoxycholzuur Glenmark.

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

Important identified risks	• Diarrhoea • Biliary colic • Decompensation of hepatic cirrhosis in patients with advanced stage of primary biliary cirrhosis • Hypersensitivity and skin reactions
Important potential risks	• Teratogenicity
Missing information	• Off-label use in patients with radio-opaque calcified gallstones, occlusion of the biliary tract, frequent episodes of biliary cholic and impaired contractility of the gall bladder • Off-label use n patients with acute inflammation of the gall bladder or biliary tract • Off-label use in children with biliary atresia following unsuccessful portoenterostomy or without recovery of good bile flow • Safety in breastfeeding

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 Ursochol. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test with two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and

applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ursodeoxycholzuur Glenmark 150 mg, 300 mg, and 450 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Ursochol 150 mg, 300 mg, and 450 mg tablets. Ursochol 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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ursodeoxycholzuur Glenmark with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 April 2018.

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