CBG MEB

Public Assessment Report

Scientific discussion

Ursodeoxycholzuur Glenmark 250 mg hard capsules

(ursodeoxycholic acid)

NL/H/3565/001/DC

Date: 23 May 2017

This module reflects the scientific discussion for the approval of Ursodeoxycholzuur Glenmark 250 mg hard capsules. The procedure was finalised on 28 September 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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
PBC	Primary Biliary Cirrhosis
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UDCA	Ursodeoxycholic Acid

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ursodeoxycholzuur Glenmark 250 mg hard capsules, from Glenmark Pharmaceuticals Europe Limited.

The product is indicated:

- For the dissolution of cholesterol gallstones in the gall bladder. The gallstones must not show as shadows on X-ray images and should not exceed 15 mm in diameter. The gall bladder must be functioning despite the gallstone(s).
- For the treatment of primary biliary cirrhosis (PBC), provided there is no decompensated hepatic cirrhosis.

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

This decentralised procedure concerns a bibliographical application based on well-established medicinal use of ursodeoxycholic acid (UDCA) capsules. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the Marketing Authorisation Holder (MAH) can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. “Medicinal use” does not exclusively mean “use as an authorised medicinal product’’, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the MAH should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

UDCA in general has been used in clinical practice for over 20 years. In the Netherlands, Ursochol tablets and Ursofalk capsules have been registered since 1979 and 1980, respectively. Also in the CMS countries, UDCA has been registered for 10-20 years. The use of UDCA in the proposed indications has been sufficiently substantiated and can be considered well-established. Additionally the MAH provided a bioequivalence study with Ursodeoxycholzuur Strides 250 mg versus Ursofalk 250 mg capsules from the Australian market. The acceptability of a bioequivalence study in the context of a well-established use application was questioned by one CMS, as well as the relevance of a reference product from the Australian market. These issues were resolved.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application. The results of a bioequivalence study were however provided in support of this application.

The marketing authorisation was granted based on article 10a of Directive 2001/83/EC.

The concerned member states (CMS) involved in this procedure were Czech Republic, Poland and the Slovak Republic.

II. QUALITY ASPECTS

II.1 Introduction

Ursodeoxycholzuur Glenmark is a hard gelatin capsule with two tightly closed, orange-opaque coloured parts (cap and body) containing a white or almost white granular powder. Each hard capsule contains 250 mg ursodeoxycholic acid.

The capsule are packed in PVC-PVDC/Aluminium blisters

The excipients are:
Capsule content – maize starch, pregelatinised starch, crospovidone (E1202), sodium lauryl sulphate, anhydrous colloidal silicon dioxide and magnesium stearate (E572).
Capsule shell – gelatin (E441), sunset yellow (E110) and titanium dioxide (E171).

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 a white or almost white crystalline powder, which is practically insoluble in water, freely soluble in ethanol, slightly soluble in acetone and practically insoluble in methylene chloride. Ursodeoxycholic acid presents 10 chiral centres. It does not exhibits polymorphism.

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. Description and validation of the micronization process is provided as this is not covered by the CEP.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and an additional requirement of the CEP. Batch analytical data demonstrating compliance with this specification have been provided for one full scale batch.

Stability of drug substance
Assessment thereof was not part of granting the CEP and has been granted by the EDQM. The active substance is stable for 5 years when stored under the stated 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. All excipients are well known.
This product concerns an abridged, bibliographic application for UDCA 250 mg capsules submitted under Article 10a (well-established use) of Directive 2001/83/EC for which bioequivalence studies are not required. However, the MAH submitted the results of a bioequivalence study comparing Ursodeoxycholic acid Strides 250 mg capsules to Ursofalk 250 mg capsules from the Australian market.
Comparative dissolution studies between Ursodeoxycholic acid Strides 250 mg capsules and Ursofalk from the European market were conducted. The results show that the dissolution profiles of test and reference are comparable.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines and includes weighing, wet granulation, disintegration, blending, filling of the capsules and packaging. The product process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with their respective Ph.Eur monographs. 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 description, identification, average mass, uniformity of dosage units, dissolution, water content, assay, impurities, residual solvents and microbiological limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The release and shelf-life requirements limits for all tests are the same. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided on three batches, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches stored at 25°C/60% RH (36 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. No significant changes or trends occur in the parameters tested when the capsules are stored at accelerated conditions during 6 months and during the 36 months of storage under long term conditions. Photostability studies show that the product is not sensitive for light degradation. On basis of the data submitted, a shelf life was granted of 36 months.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Gelatin is the only excipient used of animal origin (bovine). A relevant TSE Certificate of Suitability of the gelatin supplier used in the manufacture of the capsules is provided and considered acceptable.

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

According to Article 10a of Directive 2001/83/EC, it is possible to replace results of pre-clinical trials by detailed references to published scientific literature (information available in the public domain), if it can be demonstrated that the active substance has been in well-established medicinal use within the Community for at least 10 years for the same indication, with recognized efficacy and an acceptable level of safety.

The active compound of UDCA Tramedico tablets is ursodeoxycholic acid. This compound is a gallstone dissolving agent, which acts by reducing the content of cholesterol in bile, due either to a reduction in hepatic cholesterol synthesis or reduced absorption of cholesterol or both. The provided non-clinical overview is adequate.

In the Netherlands, ursodeoxycholic acid is a well-known active substance in medicinal products for treatment of biliary cirrhosis and for the dissolution of small and medium sized cholesterol-rich gallstones. These products include, among others, Ursochol 150, 300, 450 mg, tablets (NL License RVG 07718, 09307, 29828) and Ursofalk capsules 250 mg (RVG 08384). Both are registered products in the Netherlands for more than ten years.

The provided literature data justify 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.

III.1 Environmental risk assessment

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. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of ursodeoxycholic acid are well known. As ursodeoxycholic acid is a widely used, well-known active substance. The MAH has not provided additional studies and further studies are not required.

IV. CLINICAL ASPECTS

UDCA is a well-known active substance with established efficacy and tolerability.
The dossier is based on well-established use of UDCA. The MAH summited a clinical overview for the justification of the proposed indications and posology. Sufficient literature references were provided.

IV.1 Pharmacokinetics

UDCA is a bile acid which causes 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) dissolution in the proximal jejunum takes place through solubilisation in small micelles with other bile acids. UDCA is only absorbed systemically to a small extent and is considered not to act systemically. However UDCA levels can be used to show a comparable absorption of UDCA from different formulations.
Reference is made to several UDCA formulations. The MAH indicated that the bioavailability of UDCA from a 250 mg capsules was assessed in one clinical study in 64 healthy subjects and results demonstrated bioequivalence for the UDCA Strides capsules formulation against the innovator Ursofalk capsules, Australia. The study of Williams et al. showed pharmacokinetics of 4 different UDCA formulations marketed in the US and Canada. Unfortunately, compositions of these formulations are lacking. Though a considerable variability in pharmacokinetics was apparent, systemic exposure for the US, Canadian and Ursolvan product was comparable. These data indicate that the small difference in composition between Ursodeoxycholzuur Glenmark 250 mg hard capsules and Ursofalk 250 mg capsules are unlikely to affect the absorption in a clinically relevant way. For this well established application the MAH supported that the data obtained with the different formulations can be bridged to the current formulation. Taking into account the small difference in composition between the UDCA Glenmark 250 mg capsule and Ursofalk 250 mg capsule and taking into account the comparable dissolution at pH 1.2, 4.5, 6.8, 7.5 and 8.4, a clinically relevant difference in bioavailability is not expected.

IV.2 Pharmacodynamics

The MAH submitted an overview of literature data on the pharmacodynamics of UDCA. This is considered sufficient given that this is a bibliographic application and that UDCA is a well-known active substance. Based upon this overview, no concerns are raised. UDCA induces changes in bile acid composition and reduces cholesterol in bile, but the exact mechanism of UDCA in the dissolution of gallstones and treatment of PBC has not been fully elucidated.

IV.3 Clinical efficacy

To substantiate clinical efficacy of this application based on well-established use, the MAH submitted a literature overview including 60 references between up to 2013.

<u>Efficacy of UDCA in the dissolution of gallstones</u>
During the past 20 years, better understanding of the pathogenesis of cholesterol gallstone disease has led to alternative nonsurgical methods for treating gallstones in selected groups of patients. Use of 2 naturally occurring bile acids, chenodeoxycholic acid (CDCA) and ursodeoxycholic acid (UDCA), were reported in 1972 and 1975, respectively, for successful dissolution of cholesterol gallstones in humans.
Cholesterol gallstones should not be visible on a plain X-ray (radiolucent) and be no larger than 15 mm in diameter because they will not dissolve with ursodeoxycholic acid. The gallbladder should be

functional despite the gallstone(s). The recommended dose for the cholesterol stones is 10 mg/kg per day. The proposed mechanism of action involves unsaturation of bile by UDCA leading to gallstone dissolution by solubilising cholesterol from the stone surface.
One of the main problems of bile acid therapy is that dissolution of gallstones is a very slow process (about 1 mm/month).

Efficacy of UDCA in primary biliary cirrhosis
The only widely accepted treatment for PCB is UDCA. It is the only treatment aimed at modifying the natural history of the disease recommended in guidelines issued by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver.
UDCA at doses of 10 to 15 mg/kg/d in all studies examined showed improvements in biochemical tests of the liver and in liver histological condition of PBC. Recent reports have demonstrated the favourable effects of UDCA on long-term survival in patients with PBC receiving standard doses (13–15 mg/kg/d) over 10–20 years. Treatment with UDCA led to a transplant-free survival similar to that of a healthy control population matched for age and gender in patients with early-stage disease and to improved survival in comparison to the estimated survival at the start of treatment.

IV.4 Clinical safety

UDCA is well tolerated. The safety profile is comparable for both the standard and high-dose regimens, as initially demonstrated in studies of varying dosing regimens in PBC. No significant side effects or drug toxicity have been demonstrated across the many standard and high-dose UDCA trials.
Diarrhoea was the most frequent adverse event during UDCA treatment. One review suggested an "unanticipated" UDCA toxicity including hepatitis, pruritus, cholangitis, ascites, vanishing bile duct syndrome, liver cell failure, death, severe watery diarrhoea, pneumonia, dysuria, immune-suppression, mutagenic effects and withdrawal syndrome upon sudden halt.
Long-term use of high-dose UDCA might be associated with an increased risk of colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. After the start of UDCA, the annual incidence of colonic carcinomas increased up to 6 years and subsequently decreased.

There are no adequate data on the efficacy and safety of UDCA in children.
Drug interactions are mainly related to drug absorption. However, recent evidence suggests that UDCA may interact with other drugs via the induction of CYP3A isoforms.

IV.5 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.

- 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 biliary tract, frequent episodes of biliary colic and impaired contractility of the gall bladder - Off-label use in 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.6 Discussion on the clinical aspects

UDCA has been used and is registered for the requested indications in the RMS and the CMS countries for 10-20 years. Based upon clinical data and the longstanding clinical experience, the use of UDCA in the proposed indications can be considered well-established with demonstrated efficacy. The proposed dose for both indications is in line with current recommendations. On the basis thereof, the efficacy of Ursodeoxycholzuur Glenmark 250 mg hard capsules can be considered acceptable.

The safety profile of UDCA in the proposed indications can be considered well-established and acceptable. The proposed posology for both indications is in line with current recommendations. The adverse events of UDCA are well characterised and adequately covered by the SmPC's of currently available UDCA products.

V. USER CONSULTATION

The package leaflet 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. Twenty-two participants were tested in one pilot round with two participants, followed by two rounds with ten participants each. The readability, clarity, graphical layout and font style and size of the text are acceptable.
Overall, the results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ursodeoxycholzuur Glenmark 250 mg hard capsules has a proven chemical-pharmaceutical quality. The documentation in relation to this product is of sufficiently high quality in view of the European regulatory requirements.

From a clinical point of view, the proposed indications of dissolution of radiolucent gallstones and PBC, as well as the proposed posology are in line with current ursodeoxycholic acid use and recommendations in the RMS and CMS countries, in which ursodeoxycholic acid has been registered for 10-20 years. Based upon clinical data and the longstanding clinical experience, the use of ursodeoxycholic acid in the proposed indications can be considered well-established with demonstrated efficacy and acceptable safety.

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 member states, on the basis of the data submitted, considered that a bioequivalence study can be considered supportive in the context of a well-established use application, and the Australian reference product used has been demonstrated to be relevant for the EU market. The decentralised procedure was finalised with a positive outcome on 28 September 2016.

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