

Public Assessment Report

Scientific discussion

Ursochol 600, tablets 600 mg

(ursodeoxycholic acid)

NL License RVG: 114131

Date: 16 November 2015

This module reflects the scientific discussion for the approval of Ursochol 600, tablets 600 mg. The marketing authorisation was granted on 20 October 2014. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Ursochol 600, tablets 600 mg from Zambon Nederland B.V.

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.
 - primary biliary cirrhosis (PBC)
- Paediatric patients
- Hepatobiliary disorders associated with cystic fibrosis in children and adolescents aged 6-18 years.

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 Ursochol 150 mg, 300 mg and 450 mg tablets (NL license RVG 07718, 09307 and 29828), which have been registered in the Netherlands by Zambon Nederland B.V. since 7 February 1979, 6 June 1982 and 4 April 2005, respectively. With this application an additional strength is introduced: a 600 mg tablet. The addition of a 600 mg dose fits into the SmPC dose recommendations, in which a dose of 600 mg can be administered.

The marketing authorisation has been granted pursuant to 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 previously performed with Ursochol.

No paediatric development programme has been submitted, as this is not required for a line extension.

II. QUALITY ASPECTS

II.1 Introduction

Ursochol 600 is a white capsule shaped tablet tablets scored on one side. The tablets can be divided into equal halves. Each tablet contains 600 mg of ursodeoxycholic acid.

The tablets are packed in aluminium/PVC blisters.

The excipients are: lactose monohydrate, povidone (E1201) crospovidone (E1202) and magnesium stearate (E572).

II.2 Drug Substance

The active substance is ursodeoxycholic acid an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder, which is practically insoluble

in water, freely soluble in ethanol (96 per cent), slightly soluble in acetone and practically insoluble in methylene chloride. No polymorphism has been observed for UDCA.

The CEP procedure is used for the two 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. and the additional specifications of the CEPs. Batch analytical data demonstrating compliance with the drug substance specification have been provided for a total of 5 production-scale batches.

Stability of drug substance

The active substance of the first manufacturer is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM. For the second manufacturer, stability data on the active substance have been provided for six commercial-scale batches stored at 25°C/60%RH for up to 60 months and at 40°C/75%RH for up to 6 months. On the basis of data included in the dossier the claimed re-test period of 5 years, without storage restriction can be granted.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The current strength is an addition to the range of other strengths marketed by the MAH (150 mg, 300 mg and 450 mg). The drug product is fully dose proportional to the other three strengths. No clinical studies with the proposed strength have been performed, instead dissolution was examined at various pHs, and compared with the dissolution profile of the other three strengths.

At the lower pH values (pH 1.2 and 4.5) the active substance is not dissolved and at pH 3.8 only up to ± 40% is dissolved, where the dissolution profiles of the 300 mg and the 600 mg strength are demonstrated to be similar. In the release medium, buffer pH 8.0, all four tablet strengths fully and rapidly dissolve (> 85% in 15 minutes). At pH 6.8 the dissolution is more critical where it was adequately demonstrated that the dissolution profiles of all tablet strengths are comparable. For the 150 mg strength 4 tablets per vessel were used in order to create a similar critical system.

The manufacturing process of the proposed formulation has been developed on the basis of the experience gained on the homothetic formulation of Ursochol 150 mg tablets.

Since the tablets contain a score line it was adequately demonstrated that the tablets can be broken in a reproducible way.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The selected manufacturing process is a conventional one consisting of the following steps: sieving and mixing of ursodeoxycholic acid and povidone, wet granulation of the mixture (with water as granulation fluid), final blending with the other excipients and compression.

The manufacturing process will be validated on the first three industrial scale batches. An acceptable validation protocol is available. Since the manufacturing process is seen as a standard process and given that the MAH already has experience with the manufacturing of the other three fully dose proportional (lower) strengths, the omission of validation data at the time of submission is accepted.

Control of excipients

The excipients comply with the Ph.Eur. For lactose monohydrate the particle size (functionality-related characteristic) is included in the specification. The specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, assay, degradation, uniformity of mass, disintegration, dissolution and microbiological quality. The release and shelf-life requirements/limits are identical, and they are acceptable.

The analytical methods have been adequately described and validated. For the method for microbiological quality it has been demonstrated that no inhibition of bacterial growth occurs.

Batch analytical data from the proposed production site has been provided on three pilot-scale batches demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided for three pilot-scale batches stored 25°C/60%RH (24 months), 30°C/65%RH (24 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 in Al-PVC blisters, the proposed commercial primary packaging material. At all three temperatures no changes, other than analytical variance, are observed during the storage periods.

On the basis of the provided stability data the claimed shelf-life of 24 months can be granted. The drug product was shown to be photostable.

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

Certificates of suitability issued by the EDQM have been provided for the active substance. The CEP also covers the TSE safety of the drug substance by specifying the nature of the animal tissue used (bovine bile) and the countries of origin of the source material. For lactose the requirements of the Ph.Eur. on TSE are fulfilled.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Ursochol 600, tablets 600 mg 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)

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.

III.2 Discussion on the non-clinical aspects

This product is a line extension to Ursochol tablets, 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 previously registered strengths. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Ursodeoxycholic acid is a well-known active substance with established efficacy and tolerability. The application concerns a line extension of Ursochol a 600 mg tablet to the registered 150, 300 and 450 mg tablets. The addition of a 600 mg dose fits it into the SmPC dose recommendations, in which a dose of 600 mg can be administered. 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 MEB agrees that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

The composition of the 600 mg tablet is dose proportional to the 150, 300 and 450 mg tablets. The tablet is manufactured by the same manufacturer and manufacturing process. Dissolution data have been provided at pH 6.8 and 8, as at lower pH ursodeoxycholic acid does not dissolve, which is acceptable. For dissolution, the 300 mg tablet (2x) has been compared to the 600 mg tablet. Dissolution was comparable. In addition the dissolution characteristics of the 600 mg strength are comparable with the strengths of 150 mg (4 tablets) and 450 mg.

Considering the fact that the 600 mg tablet covers the already existing recommended dose, and taking into account the pharmacokinetics of UDCA, suggesting a less than dose proportional increase in AUC at higher doses, supportive dissolution data for an additional strength in accordance with the guideline on bioequivalence are considered sufficient. The biowaiver for the additional strength is considered acceptable. A bioequivalence study is not required.

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 Ursochol.

Summary of safety concerns	
Important identified risks	<p>Drug-induced gastrointestinal disorders (diarrhoea)</p> <p>Hypersensitivity and skin reactions</p> <p>Decompensation of hepatic cirrhosis during therapy of the advanced stages of primary biliary cirrhosis</p>
Important potential risks	Foetal malformations and pre-/post-natal developmental effects
Missing information	<p>Off-label use in patients with radio-opaque calcified gallstones, occlusion of the biliary tract, frequent episodes of biliary colic and impaired contractility of the gallbladder, acute inflammation of the gallbladder or the biliary tract</p> <p>Off-label use in children with biliary atresia following unsuccessful portoenterostomy or without recovery of good bile flow</p> <p>Off-label use in children with biliary atresia</p> <p>Use in breastfeeding women</p>

The MEB 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 previously registered strengths of Ursochol tablets. No new clinical studies were conducted. The MAH demonstrated similarity to the 150 mg, 300 mg and 450 mg tablets strengths based on *in-vitro* data. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet (PL) has not been evaluated via a user consultation study. The information on the 600 mg formulation is added to the approved PL for the lower Ursochol strengths. There will be no significant changes to the content of the leaflet, and the layout and style remain unchanged. It is agreed that separate user testing is not required for this line extension.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ursochol 600 mg tablets has a proven chemical-pharmaceutical quality and is an approvable line extension to Ursochol 150 mg, 300 mg and 450 mg tablets, a well-known medicinal product with an established favourable efficacy and safety profile.

No comparative bioavailability study is deemed necessary, as the conditions for a biowaiver are fulfilled. The 600 mg dose fits into the range of the dose recommendation for UDCA.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Ursochol 600 mg tablets was authorised in the Netherlands on 20 October 2014.

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