COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ursodeoxycholzuur 450 mg Zambon, tablets

(ursodeoxycholic acid)

NL Licence RVG 126236

Date: 4 March 2021

This module reflects the scientific discussion for the approval of Ursodeoxycholzuur 450 mg Zambon, tablets. The marketing authorisation was granted on 14 October 2020. 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
EDQM	European Directorate for the Quality of Medicines
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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Ursodeoxycholzuur 450 mg Zambon, tablets from Zambon Nederland B.V.

The product is indicated for:

- dissolution of cholesterol gallstones in patients
  - with one or more radiolucent (X-ray negative) 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 cholangitis

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.

This national procedure concerns a generic application claiming essential similarity with the innovator product Ursochol 450 tablets (NL Licence RVG 29828) which has been registered in the Netherlands by Zambon Nederland B.V. since 4 April 2005.

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

II. QUALITY ASPECTS

II.1 Introduction

Ursodeoxycholzuur 450 mg Zambon is a white capsule shaped tablet containing 450 mg of ursodeoxycholic acid.

The tablets are packed in PVC/aluminium blisters.

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

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 powder and is practically insoluble in water, freely soluble in ethanol (96 per cent), slightly soluble in acetone and practically insoluble in methylene chloride.

The CEP procedure is used for both 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 Ph.Eur.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specifications are in line with the CEPs. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production scaled batches per supplier.

Stability of drug substance
The retest period of the substance manufactured by the first manufacturer is 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.
Stability data on the drug substance from the second manufacturer have been provided on 6 production-scale batches stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). No trends or out-of-specification results are observed at long term or accelerated conditions. The proposed retest period of 60 months is acceptable.

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 MAH currently has four different strengths of Ursochol tablets (ursodeoxycholic acid) registered: a presentation of 150 mg, one of 300 mg, one of 450 mg and one of 600 mg, under the trade name Ursochol. The registered strengths have the exact same composition, only the tablet size is different. Since 450 mg tablets of the current process are already registered, it is acceptable to provide comparative dissolution data with

this strength in order to justify not performing a bioequivalence study. Sufficient comparative dissolution data have been provided (see section IV.2 'Pharmacokinetics).

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, final blending and compression. 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.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for six full-scale batches.

Control of excipients

The excipients comply with Ph.Eur. requirements. In general, these specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identification, uniformity of mass, disintegration, dissolution, assay, related substances microbiological purity and uniformity of dosage units. With the exception of uniformity of mass which is not tested at shelf life, the release and shelf life specifications are similar. In general the justification of the specification parameters and limit are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on six production-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three production batches stored at 25°C/60% RH (36 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 Al-PVC blisters. All three batches at long-term and accelerated conditions remained within the specifications. Based on the provided data the proposed shelf life of 3 years without special storage conditions has been granted.

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

Compliance of the drug substance with Ph.Eur. monograph "Products with risk of transmitting agents of animal spongiform encephalopathies" no. 1483 is stated. The nature of the animal tissue used in the manufacture of the drug substance is bovine bile.

There are no excipients 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. Magnesium stearate is of vegetable origin.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Ursodeoxycholzuur 450 mg Zambon 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 450 mg Zambon 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 MEB 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 MEB agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

The MAH has four different strengths of ursodeoxycholic acid (Ursochol) tablets registered: a 150 mg, 300 mg, 450 mg and 600 mg strength. The composition of the lower two presentations is proportional. The MAH provided comparative dissolution data for Ursodeoxycholzuur 450 mg Zambon with the registered formulation in order to justify not performing a bioequivalence study. The provided dissolution profiles are performed at 75

rpm instead of the 50 rpm as stated in the Guideline on the investigation of bioequivalence. This is however considered acceptable, since the drug products have the same:

- qualitative and quantitative composition
- drug substance
- manufacturing site
- manufacturing process and equipment
- excipients
- quality controls.

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 450 mg Zambon.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	• Drug-induced gastrointestinal disorders (diarrhoea) • Hypersensitivity and skin reactions • Decompensation of hepatic cirrhosis during therapy of the • advanced stages of primary biliary cirrhosis • Biliary colic • Use in breastfeeding women
Important potential risks	• Foetal malformations and pre-/post-natal developmental effects
Missing information	• 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 • Off-label use in children with biliary atresia following unsuccessful portoenterostomy or without recovery of good bile flow • Off-label use in children with biliary atresia • Use in breastfeeding women

The MEB agrees 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. Equivalence has been demonstrated based on chemical-pharmaceutical characteristics. 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 not been evaluated via a user consultation study. The content of the proposed PL is the same as the currently approved PL of the four existing strengths of Ursochol. The PL for Ursodeoxycholzuur 450 mg Zambon was not changed, except that the posology text was simplified to the dosing scheme the 450 mg tablet. The MEB agreed that separate user testing was not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ursodeoxycholzuur 450 mg Zambon has a proven chemical-pharmaceutical quality and is a generic form of Ursochol 450 mg. Ursochol is a well-known medicinal product with an established favourable efficacy and safety profile.

Equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. A biowaiver has been granted.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for this medicine with the reference product, and has therefore granted a marketing authorisation. Ursodeoxycholzuur 450 mg Zambon was authorised in the Netherlands on 14 October 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Product Information affected	Date of end of the procedure	Approval/ non approval	Summary/ Justification for refuse