Public Assessment Report

Scientific discussion

Ursochol
(ursodeoxycholic acid)

SE/H/1318/01-02/DC

This module reflects the scientific discussion for the approval of Ursochol. The procedure was finalised at 2014-06-04. For information on changes after this date please refer to the module ‘Update’.
I. INTRODUCTION

The application for Ursochol, 250 mg and 500 mg hard capsules is a generic application made according to Article 10(1) of Directive 2001/83/EC. In CMS Norway the application for Ursochol, 500 mg capsule, hard is a hybrid application according to Article 10(3) of Directive 2001/83/EC, as the Ursofalk 500 mg film-coated tablet reference product is not authorised in Norway. The applicant, Orifarm Generics A/S, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, IS 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, hard capsule, authorised in Sweden since 1995, with Dr. Falk Pharma GmbH as marketing authorisation holder.

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

For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Ursochol is presented in the form of hard capsules containing 250 and 500 mg of ursodeoxycholic acid. The excipients are magnesium stearate, maize starch, colloidal anhydrous silica, titanium dioxide and gelatin. The capsules are packed in PVC/Al blisters.

II.2 Drug Substance

Ursodeoxycholic acid has a monograph in the Ph Eur.

Ursodeoxycholic acid is a white or almost white powder which is practically insoluble in water, freely soluble in ethanol (96 per cent), slightly soluble in acetone, practically insoluble in methylene chloride. The structure of ursodeoxycholic acid has been adequately proven and its physico-chemical properties sufficiently described. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

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

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.
II.3 Medicinal Product

Ursochol, 250 mg and 500 mg hard capsules are formulated using excipients described in the current Ph Eur. All raw materials used in the product are of vegetable origin or has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

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 under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, with no special storage precautions.

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

Ursodeoxycholic acid (UDCA) also referred to as ursodiol in the literature, is an endogenous, hydrophilic, dihydroxy bile acid.

Oral administered UDCA is quickly absorbed through passive transport in the jejunum and the upper part of ileum in the small intestines and by active transport in the lower part of ileum in the small intestines. According to the SmPC of the Swedish originator, the degree of absorption is dose-dependent and decreases with increasing doses. After absorption the bile acid is almost completely conjugated with the amino acids glycine and taurin in the liver and is then excreted with the bile. First pass metabolism in the liver in the interval of 50-75%.

Depending on the daily dose and the underlying disease or the condition of the liver the more hydrofile UDCA is accumulated in bile. Concomitantly a decrease in other more lipophile bile acids has been observed.

Intestinal bacteria impact the incomplete degradation to 7-ketolithocholic acid and lithocholic acid. The biological half-life for UDCA is 3.5 to 5.8 days.
Bioequivalence study

Bioequivalence was evaluated in one single-dose, two-way crossover study conducted in 48 healthy volunteers, comparing Ursochol, 2x250 mg, capsule with Ursofalk, 2x250 mg, capsule under fasting conditions. Blood samples were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of un-conjugated ursodiol, conjugated glycoursoodiol and conjugated tauroursodiol were determined with an adequately validated LC/MS/MS method. Given that ursodiol is an endogenous substance both baseline-corrected and uncorrected data were presented. In all analyses, i.e. un-conjugated, conjugated and total ursodiol, both baseline corrected and uncorrected, the 90% confidence interval for the AUC$_{0-t}$ and C$_{max}$ ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%. Baseline-corrected un-conjugated ursodiol is considered to be the most relevant parameter in the bioequivalence evaluation. The results of baseline-uncorrected analysis of ursodiol and the results of analyses of total conjugated ursodiol are considered to be supportive.

Biowaiver for additional strength

The biowaiver for the 500 mg capsule is considered to be adequately justified since a dose of 500 mg was used in the bioequivalence study and since both strengths are made from one common blend.

Published data regarding linearity of UDCA pharmacokinetics is limited. According to the originator’s SmPC, the degree of absorption is dose-dependent and decreases with increasing doses. It appears to be some degree of non-linear pharmacokinetics, but due to limited and variable data it is difficult to conclude how large the non-linearity is. However, data indicate that the non-linearity might not be too pronounced. In the current bioequivalence study, the AUC and Cmax point estimates were close to 1 and it is therefore considered unlikely that results from a study with a 250 mg dose would be shifted to such an extent that a different bioequivalence conclusion would be drawn. To summarize, although it appears to be some degree of non-linearity in UDCA pharmacokinetics, the dose of 2x250 mg used in the bioequivalence study is acceptable for UDCA being an endogenous substance. Thus, the lack of studies using 1x250 mg is accepted.

Pharmacokinetic conclusion

Bioequivalence has been sufficiently demonstrated.

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.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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 Ursosan, 250 mg capsules hard. The user test of the Ursosan, 250 mg capsules hard leaflet was assessed and accepted in the national Swedish procedure, 111:2006/59240 (asp. no: 2006-1136). The bridging report submitted by the applicant has been found acceptable.
The results of the conducted bioequivalence study can be extrapolated to other strengths since the criteria for biowaiver for additional strengths are fulfilled according to the Guideline on the investigation of bioequivalence.

The risk/benefit ratio is considered positive and Ursochol, 250 mg and 500 mg, hard capsules are recommended for approval.

VI. APPROVAL

The Decentralised procedure for Ursochol, 250 mg and 500 mg, hard capsules was successfully finalised on 2014-06-04.
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