COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ursodeoxycholzuur PI 250 mg and 500 mg hard capsules (ursodeoxycholic acid)

NL/H/5656/001-002/DC

Date: 19 January 2026

This module reflects the scientific discussion for the approval of Ursodeoxycholzuur PI 250 mg and 500 mg hard capsules. The procedure was finalised on 1 May 2024. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 PI 250 mg & 500 mg hard capsules, from Pharmaceutical Innovation Services S.L.

The product is indicated for:

1. The dissolution of cholesterol gallstone in patients:
   - having one or more radiolucent (radio-negative) gallstones, preferably with a diameter of no more than 2 cm, in a properly functioning gallbladder.
   - refusing surgical intervention or for whom surgical procedures are not indicated.
   - in whom cholesterol supersaturation has been demonstrated by chemical testing on bile obtained via duodenal drainage.
   - as adjuvant medicine before and after gallstone shockwave dissolution (lithotripsy).
2. Primary biliary cholangitis (PBC, also known as primary biliary cirrhosis).

<u>Paediatric population</u>

3. Hepatobiliary disorder associated with cystic fibrosis in children and adolescents aged 6 to less than 18 years.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC, which concerns a generic application.

In this decentralised procedure, essential similarity is proven between the new product and two European Reference Products (ERPs). Ursofalk 250 mg capsule hard is used as ERP for the 250 mg strength in the concerned member states (CMS) Greece and Spain. For the 500 mg strength, Ursofalk 500 mg film-coated tablet is used as ERP in all CMSs. Ursofalk 250 mg and 500 mg have been registered in the Netherlands via national procedures (RVG 08384 and RVG 112405) since 14 November 1980 and 16 May 2013, respectively.

The use of Ursofalk 500 mg film-coated tablet as reference product is considered acceptable. Section 5.3.2.1 of the Notice to Applicants states:
"Directive 2001/83/EC defines a generic medicinal product in Article 10(2)(b) as a medicinal product which has:
· the same qualitative and quantitative composition in active substances as the reference medicinal product,
· the same pharmaceutical form as the reference medicinal product,
· and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies."

Furthermore, section 5.3.2.1 gives a definition of 'same pharmaceutical form': *"A generic product and a reference product may be considered to have the same pharmaceutical form if*

they have the same form of administration as defined by the Pharmacopoeia. Furthermore, Article 10(2)(b) of the amended Directive provides that the various immediate release oral forms, which would include tablets, capsules, oral solutions and suspensions, are considered to be the same pharmaceutical form for the purposes of Article 10."

The pharmaceutical form "hard capsules" and the pharmaceutical form of the reference product Ursofalk 500 mg "film-coated tablets" can therefore be considered to be the same pharmaceutical form for submission under article 10.1.

The concerned member states (CMS) involved in this procedure were Austria, Bulgaria, Greece, Poland, Portugal, Romania and Spain.

Similarity assessment

According to Article 8(1) of Regulation (EC) No 141/2000, no marketing authorisation can be granted for a product similar to an orphan medicinal product for a period of ten years, when this concerns a similar medicinal product with the same therapeutic indication (PBC). A similarity assessment has been performed between Ursodeoxycholzuur PI and Ocaliva, which obtained orphan market exclusivity on 12 December 2016, based on designation EMA/96192/2018. The similarity assessment report was completed in March 2023, concluding the two products were not similar based on therapeutic indication (PBC) and mechanism of action. This was reflected in the indications and the procedure was therefore acceptable.

II. QUALITY ASPECTS

II.1 Introduction

Ursodeoxycholzuur PI is a hard capsule.

Ursodeoxycholzuur PI 250 mg

Ursodeoxycholzuur 250 mg hard capsules are approximately 21.7 mm x 7.64 mm, with a yellow cap and body filled with white homogeneous powder.

Each capsule contains 250 mg of ursodeoxycholic acid as the active substance.

The excipients are: maize starch, silica colloidal anhydrous (E551), magnesium stearate (E470b), gelatine (E441), titanium dioxide (E171) and yellow iron oxide (E172).

Ursodeoxycholzuur PI 500 mg

Ursodeoxycholzuur 500 mg hard capsules are 23.4 mm length with white cap and body filled with white homogeneous powder.

Each capsule contains 500 mg of ursodeoxycholic acid as the active substance.

The excipients are: maize starch, silica colloidal anhydrous (E551), magnesium stearate (E470b), gelatine (E441) and titanium dioxide (E171).

The two capsule's content are dose proportional.

The hard capsules are packed in polyvinyl chloride (PVC)/Aluminium blisters.

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. No polymorphic forms are known.

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.

Manufacturing process
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 and is in line with the CEP with additional tests for microbial control and particle size distribution which is relevant in view of the poor solubility of the drug substance. Batch analytical data demonstrating compliance with this specification have been provided for three pilot scaled batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development
The formulation development of the 250 mg strength was based on the reference product Ursofalk 250 mg capsules, which was characterised by the MAH. In addition a Ursodeoxycholzuur 500 mg capsule was developed essentially similar to Ursofalk 500 mg film coated tablets. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for six full scaled batches (two

batches per strength) in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with Ph. Eur. and in-house requirements (for the capsule shells). 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, average mass, uniformity of dosage units, dissolution, microbial limits, powder appearance, water content, identification, content and related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three minimum and three maximum scaled batches per strength and two pilot-scaled batches of the 250 mg strength after colour change from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three pilot scaled batches per strength stored at 25°C/ 60% RH (60 months) and 40°C/75% RH (6 months). Additional stability studies on two pilot scaled batches were conducted on the 250 mg strength following the change of the colour of the capsules shell from white to yellow, covering 48 months. The stability was tested in accordance with the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 60 months. No specific storage conditions needed to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM for the active substance ursodeoxycholic acid and for the excipient gelatine have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ursodeoxycholzuur PI 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 Ursodeoxycholic acid PI is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Ursofalk 250 mg capsule hard and Ursofalk 500 mg film-coated tablet which are available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 member states agreed that no further clinical studies are required, besides the one bioequivalence study, which is discussed below. In addition, a biowaiver for the 500 mg strength is performed.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ursodeoxycholzuur PI 250 mg hard capsules (Pharmaceutical Innovation Services S.L., Spain) was compared with the pharmacokinetic profile of the reference product Ursofalk 250 mg hard capsules (Dr. Falk Pharma Benelux B.V., the Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. Comparative dissolution complementary to the BE-study at three pHs have been adequately studied for the 250 mg capsules. The biowaiver of strength for the 500 mg capsules is also supported by relevant comparative dissolution data at the required three pH levels as well as two additional pH levels. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following requirements for granting the biowaiver for the 500 mg capsules based on the bioequivalence study with the lower strength of 250 mg have been met:

- waiving the higher strength is acceptable as it agrees with the CMDh Q&A on generics
- the strengths have been manufactured by the same process and manufacturer
- the compositions are qualitatively similar and dose proportional
- at pH 1.2 and 4.5, for all 250 mg and 500 mg batches the dissolution was 0% after 45 minutes, and can thus be considered similar. At pH 6.8, the calculated f_2-value was in between the acceptance criteria of 50-100%. An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar. All relative standard deviation (RSD) values are found to be less than 20% for the first point and less than 10% from second to last time point, complying with the Bioequivalence Guideline.

Bioequivalence study

Design

A single-dose, randomised, laboratory-blinded, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male and female subjects, aged 19-64 years. Each subject received a single dose (500 mg: two capsules of 250 mg) of one of the two ursodeoxycholic acid formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours after administration of the products.

The design of the study is acceptable.

Ursodeoxycholic acid may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of ursodeoxycholic acid. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

Out of the 48 included subjects, 43 subjects completed the study and were eligible for pharmacokinetic analysis. Four subjects withdrew from the study after dosing of period one and before dosing of period two due to personal reasons, and one subject was withdrawn before dosing of period two for safety reasons which were resolved after.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ursodeoxycholic acid, 500 mg under fasted conditions.

Treatment N=43	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	22069 ± 11502	-	5052 ± 1991	2.50 (0.67-5.00
Reference	22382 ± 13176	-	4996 ± 2024	2.00 (1.00-5.00)
***Ratio (90% CI)**	1.01 (0.93-1.09)	-	1.02 (0.94-1.11)	-

$AUC_{0-\infty}$	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 = 72 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study:
The 90% confidence intervals calculated for AUC_{0-t}, and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ursodeoxycholzuur PI 250 mg capsules, hard is considered bioequivalent with Ursofalk 250 mg hard capsules.

The results of the bioequivalence study with the 250 mg formulation can be extrapolated to the 500 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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 PI. At the time of approval, the most recent version of the RMP was version 1.0 dated 27 June 2023.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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 Ursofalk. 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 language used for the purpose of user testing the PL was Spanish.

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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ursodeoxycholzuur PI 250 mg & 500 mg capsules, hard have a proven chemical-pharmaceutical quality and are generic forms of Ursofalk 250 mg capsule hard and Ursofalk 500 mg film-coated tablet. Ursofalk 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ursodeoxycholzuur PI with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 May 2024.

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
NL/H/5656/001-002/IB/001/G	Change in the (invented) name of the medicinal product - for Nationally Authorised products. Introduction of , or changes to, a summary of pharmacovigilance system for medicinal products for human use - Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location.	Yes No	3-9-2025 3-9-2025	Approved Approved	N.A. N.A.
NL/H/5656/001-002/IB/002	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/ biosimilar medicinal products following assessment of the same change for the	Yes	17-10-2025	Approved	N.A.

	reference product - Implementation of change(s) for which no new additional data are submitted by the MAH.				