CBG MEB

# Public Assessment Report

# Scientific discussion

# Grinterol 250 mg hard capsules

# (ursodeoxycholic acid)

## NL/H/3712/001/DC

## Date: 10 July 2017

**This module reflects the scientific discussion for the approval of Grinterol 250 mg hard capsules. The procedure was finalised on 21 December 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 |
| 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 Member States have granted a marketing authorisation for Grinterol 250 mg hard capsules, from Akciju sabiedriba "Grindeks".

The product is indicated for:

- dissolution of cholesterol gallstones 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).
- primary biliary cholangitis (PBC, also known as primary biliary cirrhosis).

Paediatric population
Hepatobiliary disorders as a result of cystic fibrosis in children and adolescents aged 6 to 18 years.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Ursofalk 250 mg capsules, hard, which has been registered in Germany by Dr. Falk Pharma GmbH since 15 March 1999. In the Netherlands, Ursofalk 250 mg capsules has been registered since 14 November 1980 by Dr. Falk Pharma Benelux B.V.

The concerned member states (CMS) involved in this procedure were Belgium, Czech Republic, Estonia, Latvia, Poland, Lithuania, Portugal and the United Kingdom.

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

# II. QUALITY ASPECTS

## II.1 Introduction

Grinterol is a white hard gelatin capsule size 0, containing a white or almost white powder. Each hard capsule contains 250 mg ursodeoxycholic acid.

The capsules are packed in PVC/Aluminium blisters.

The excipients are:
Capsule fill – maize starch, silicon dioxide (E551) and magnesium stearate (E470B)
Capsule shell – Titanium dioxide (E171) and gelatin (E441)

## II.2 Drug Substance

The active substance is ursodeoxycholic acid, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Ursodeoxycholic acid is a white or almost white powder and freely soluble in ethanol, slightly soluble in acetone, practically insoluble in methylene chloride and water. It is a racemic mixture of R and S isomers. The product does not exhibits polymorphism and is not hygroscopic. Both CEP and ASMF procedures are used.

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.

In addition, the Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
Two active substance manufacturers are used and a combined specification is given. The manufacturing process in the CEP procedure covers the active substance from bovine bile origin. For the active substance originated from poultry bile an ASMF is submitted. The manufacturing process of the active substance originating from poultry bile, consists of two real synthesis steps. In this case this is deemed acceptable as the starting material is isolated directly from the poultry bile.

Quality control of drug substance
The applicant has provided one combined active substance specification for material obtained from both sources. In general the active substance specification is in line with the Ph.Eur. and the additional requirements of the CEP and the ASMF.
The analytical methods as used by the applicant are adequately described and validated. Batch analysis data demonstrating compliance with the drug substance specification have been provided by the drug product manufacturer for 6 batches of the drug substance.

Stability of drug substance
The active substance from bovine origin is stable for 4 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM. The active substance from poultry origin was put on stability for 5 batches at 25°C/60%RH (12 months) and 40°C°C/75RH (6 months). On basis of the data submitted a re-test period of 2 years, without specific storage conditions and when stored in the proposed packaging, can be granted.

## 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.
A bioequivalence study was performed with the reference product Ursofalk which was shown to be representative for the products marketed in the other member states included in the procedure. Comparative dissolution studies were performed between the test and reference product used in a bioequivalence study. The *in vitro* dissolution behaviour of both products is similar in all media tested.

Manufacturing process
The manufacturing process has been validated according to relevant European guidelines and includes wet mixing and granulation, drying, sieving, lubrication, capsulation, sampling and packaging. Process validation data on the product have been presented for 10 commercial scaled batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with their respective Ph.Eur monographs, or USP when no Ph.Eur monograph is available. 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 weight of the capsule content, disintegration time, dissolution, uniformity of dosage units, 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 for all parameters are identical. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 5 commercial scaled batches 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 11 commercial batches stored at 25°C/60% RH (up to 48 months), for 3 batches stored at 30°C/65%RH (12 months) and 40°C/75% RH (3 months). Bulk packaging is tested for 6 months at 25°C/60% RH. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. Stability results showed that no significant changes or trends occur in the parameters tested when the capsules are stored at long term conditions during 48 months and at intermediate conditions during 12 at 30°C. At accelerated storage at 40°C the product does not comply with the requirements regarding appearance. Data on the photostability of the drug product show that the drug product is photo stable. Therefore the proposed shelf-life of 48 months can be granted with a special precaution for storage : "Do not store above 30°C, store in the original package to protect from moisture". Since it is demonstrated that the batches comply with the dissolution limit during storage, a shelf-life of 4 years can be granted.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
TSE-CEP's have been provided for the gelatin used in the capsule shell. The material originating from bovine bile is considered to be acceptable with respect to the risk of transmitting TSE (covered by the CEP). Material originating from poultry origin has been regarded as acceptable considering the additional information with respect to the viral safety. For all excipients statements with respect to TSE safety are provided. None of these materials will pose a risk.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Grinterol 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 Grinterol 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 Ursofalk 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 member states agreed that no further non-clinical studies are required.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

Urseodeoxycholic 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 member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

## IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Grinterol 250 mg hard capsules (Akciju sabiedriba "Grindeks", Latvia) is compared with the pharmacokinetic profile of the reference product Ursofalk (Dr. Falk Pharma GmbH, Germany).

The choice of the reference product in the bioequivalence studies is justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study
*Design*
A single-dose, randomised, three-period, three-treatment, six-sequence, crossover bioequivalence study was carried out under fasted conditions in 54 healthy (26 male/28 female) subjects, aged 18-59 years. Each subject received a single dose (1000 mg; 4 x 250 mg capsule) of one of the 2 urseodeoxycholic acid formulations. The tablet was orally administered with 200 ml water. There were 3 dosing periods, separated by a washout period of 14 days.

Blood samples were collected 24, -12 and 0 hours before, and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5, 6, 8, 10, 12, 16, 24, 36, 48 and 72 after administration of the products.

The design of the study is acceptable. According to the SPmC the product should be taken with some liquid. Therefore, a study under fasted conditions is considered justified.

*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.
Plasma samples were analysed for ursodeoxycholic acid, tauro-ursodeoxycholic acid and glycol-ursodeoxycholic acid.

*Results*
One subject was withdrawn from the study due to violations of the study protocol (positive cotinine test for smoking), one subject due to personal reasons, one subject due to an adverse event and one subject was excluded for diarrhea. Therefore, 50 subjects were eligible for pharmacokinetic analysis.

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

| **Treatment N=50** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-12h}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h |
|---|---|---|---|---|
| **Test** | 54766 ± 18933 | 25804 ± 6299 | 8964 ± 3200 | 2.25 (0.50 - 6.0) |
| **Reference** | 58975 ± 25023 | 27308 ± 8262 | 10526 ± 5115 | 2.0 (0.50 – 6.0) |
| ***Ratio (90% CI)** | 0.95 (0.88 – 1.02) | -- | 0.89 (0.82 – 0.96) | -- |
| **CV (%)** | 21.7 | -- | 24.4 | -- |

**$AUC_{0-\infty}$** 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 hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life
**CV** coefficient of variation

**ln-transformed values*

Table 2. Supportive pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of corrected total urseodeoxycholic acid under fasted conditions.

| **Treatment N=50** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-12h}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h |
|---|---|---|---|---|
| **Test** | 107197 ± 30117 | 36257 ± 9454 | 10001 ± 3555 | 2.50 (0.50 – 6.0) |
| **Reference** | 112564 ± 36313 | 38447 ± 11165 | 11682 ± 5566 | 2.25 (0.50 – 6.0) |
| ***Ratio (90% CI)** | 0.96 (0.90 – 1.03) | -- | 0.89 (0.82 – 0.97) | -- |
| **CV (%)** | 19.6 | -- | 23.9 | -- |

**$AUC_{0-\infty}$** 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 hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life
**CV** coefficient of variation

**ln-transformed values*

Table 3. Supportive pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of uncorrected free urseodeoxycholic acid under fasted conditions.

| **Treatment N=50** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-12h}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h |
|---|---|---|---|---|
| **Test** | 58006 ± 20714 | 26365 ± 6412 | 9011 ± 3204 | 2.25 (0.50 – 6.0) |
| **Reference** | 62436 ± 27249 | 27929 ± 8464 | 10578 ± 5129 | 2.0 (0.50 – 6.0) |
| ***Ratio (90% CI)** | 0.95 (0.89 – 1.02) | -- | 0.89 (0.82 – 0.96) | -- |
| **CV (%)** | 20.9 | -- | 24.3 | -- |

**$AUC_{0-\infty}$** 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 hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life
**CV** coefficient of variation

**ln-transformed values*

Table 4. Supportive pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of uncorrected total urseodeoxycholic acid under fasted conditions.

| **Treatment N=50** | **$AUC_{0-t}$** ng.h/ml | **$AUC_{0-12h}$** ng.h/ml | **$C_{max}$** ng/ml | **$t_{max}$** h |
|---|---|---|---|---|
| **Test** | 117563 ± 35996 | 37982 ± 10152 | 10145 ± 3595 | 2.50 (0.50 – 6.0) |
| **Reference** | 121557 ± 41452 | 39945 ± 11666 | 11807 ± 5615 | 2.25 (0.50 – 6.0) |
| ***Ratio (90% CI)** | 0.98 (0.92 – 1.04) | -- | 0.89 (0.83 – 0.97) | -- |

| | | | | |
|---|---|---|---|---|
| **CV (%)** | 18.6 | -- | 23.7 | -- |

**$AUC_{0-\infty}$** 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 hours
**$C_{max}$** maximum plasma concentration
**$t_{max}$** time for maximum concentration
**$t_{1/2}$** half-life
**CV** coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

Based on the pivotal pharmacokinetic parameters of baseline corrected free urseodeoxycholic acid the reference and test products are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for $AUC_{(0-t)}$ and $C_{max}$ were inside the normal range of acceptability (0.80 – 1.25).
In addition, the supportive data, i.e. baseline corrected total urseodeoxycholic acid, baseline uncorrected free urseodeoxycholic acid and baseline uncorrected total urseodeoxycholic acid showed also bioequivalence between the test and reference products.

Based on the submitted bioequivalence study Grinterol is considered bioequivalent with Ursofalk.

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 Grinterol.

- Summary table of safety concerns as approved in RMP

| | |
|---|---|
| Important identified risks | - Drug-induced gastrointestinal disorders (diarrhoea)<br>- Hypersensitivity and skin reactions<br>- Decompensation of hepatic cirrhosis during therapy of the advanced stages of primary biliary cholangitis |
| 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 or the biliary tract<br>- Off-label use in children with biliary atresia<br>- Use in breastfeeding women<br>- Off-label use in patients with acute inflammation of the gall bladder or biliary tract |

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. No new clinical studies were conducted. 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 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 test has been performed in line with the guidance, and the design and layout of the leaflet is also in line with the requirements of the readability testing guideline. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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

Grinterol 250 mg hard capsules has a proven chemical-pharmaceutical quality and is a generic form of Ursofalk, 250 mg capsules. 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 Grinterol with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 21 December 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 |
|---|---|---|---|---|---|---|
| A variation in SPC and PIL to implement corrections:<br>- inclusion the term `radiolucent' instead of `non radio-opaque' in SPC section 4.1 and PIL section 1;<br>- removal of 'purified water' from the list of excipients in SPC and PIL because it is not included in final capsule mass. | NL/3712/1/IB/001 | IB | 28-03-2017 | 20-04-2017 | Approved | No |
| Change in the (invented) name of the medicinal product; for Nationally Authorised Products. | NL/3712/1/IB/002 | IB | 22-05-2017 | 12-06-2017 | Approved | No |