



## **Public Assessment Report**

### **Decentralised Procedure**

**Ursodeoxycholic acid 300 mg and 500 mg Tablets**

**(ursodeoxycholic acid)**

**Procedure No: UK/H/6671/001-002/DC**

**UK Licence Number: PL 00289/2169-2170**

**TEVA UK Limited**

## **LAY SUMMARY**

### **Ursodeoxycholic acid 300 mg and 500 mg Tablets (ursodeoxycholic acid)**

This is a summary of the Public Assessment Report (PAR) for Ursodeoxycholic acid 300 mg and 500 mg Tablets (PL 00289/2169-2170; UK/H/6671/001-002/DC). It explains how Ursodeoxycholic acid 300 mg and 500 mg Tablets were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Ursodeoxycholic acid 300 mg and 500 mg Tablets.

The products will be referred to as Ursodeoxycholic acid Tablets in this Lay Summary.

For practical information about using Ursodeoxycholic acid Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

#### **What are Ursodeoxycholic acid Tablets and what are they used for?**

Ursodeoxycholic acid Tablets are 'hybrid medicines'. This means that they are similar to a 'reference medicine' containing the same active substance, already authorised in the European Union (EU), called Destolit<sup>®</sup> 150mg Tablets (PL 00322/0076; Norgine Limited, UK) but are available in different strengths.

Ursodeoxycholic acid is a chemical present naturally in the body and it helps to control the amount of cholesterol in the blood. Ursodeoxycholic acid Tablets help dissolve gallstones not larger than 15 mm in diameter, that are made mainly of cholesterol.

#### **How do Ursodeoxycholic acid Tablets work?**

This medicine contains the active ingredient, ursodeoxycholic acid, which is one of a group of medicines used to dissolve gallstones.

#### **How are Ursodeoxycholic acid Tablets used?**

The pharmaceutical form of these medicines is a tablet and the route of administration is oral (by mouth). The dose is usually divided up and taken twice a day, with water after meals. One of the doses should always be taken after the evening meal. The tablets have a score line to help patients break the tablet if they have difficulty swallowing it whole.

The patient should always take this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

Ursodeoxycholic acid Tablets will work best if taken together with a low cholesterol and calorie-controlled diet. Patients should discuss this with their doctor.

Ursodeoxycholic acid Tablets should not be taken for more than 2 years. A regular check up will be performed by a doctor.

If patients develop diarrhoea when taking Ursodeoxycholic acid Tablets they must consult a doctor.

Ursodeoxycholic acid Tablets are not recommended in children and adolescents.

This medicine can only be obtained with a prescription.

Please read section 3 of the package leaflet for detailed dosing recommendations, the route of

administration, and the duration of treatment.

**What benefits of Ursodeoxycholic acid Tablets have been shown in studies?**

As Ursodeoxycholic acid Tablets are hybrid medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicine, Destolit<sup>®</sup> 150mg Tablets (Norgine Limited, UK). Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

With the exception of the bioequivalence studies, the applicant has not conducted any clinical trials on efficacy and/or safety for Ursodeoxycholic acid Tablets. However, reference was made to relevant published literature.

**What are the possible side effects of Ursodeoxycholic acid Tablets?**

The common side effects with Ursodeoxycholic acid Tablets (which may affect up to 1 in 10 people) are diarrhoea and pasty stools.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Ursodeoxycholic acid Tablets, see section 4 of the package leaflet available on the MHRA website.

**Why were Ursodeoxycholic acid Tablets approved?**

The MHRA decided that Ursodeoxycholic acid Tablet's benefits are greater than its risks and recommended that the products were approved for use.

**What measures are being taken to ensure the safe and effective use of Ursodeoxycholic acid Tablets?**

A risk management plan (RMP) has been developed to ensure that Ursodeoxycholic acid Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPC) and the package leaflet for Ursodeoxycholic acid Tablets including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Ursodeoxycholic acid Tablets**

The Netherlands and the UK agreed to grant Marketing Authorisations for Ursodeoxycholic acid Tablets on 02 March 2018. Marketing Authorisations were granted in the UK on 28 March 2018.

The full PAR for Ursodeoxycholic acid Tablets follows this summary.

This summary was last updated in May 2018.

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## I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Ursodeoxycholic Acid 300 mg and 500 mg Tablets (PL 00289/2169-2170; UK/H/6671/001-002/DC), are approvable. The products are prescription only medicines (POM), indicated for the dissolution of radiolucent (i.e. non-radio opaque) cholesterol gallstones not larger than 15 mm in diameter in patients with a functioning gallbladder.

The applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and The Netherlands as Concerned Member State (CMS). The applications were submitted under Article 10(3) of Directive 2001/83/EC, as amended, as hybrid applications. The reference medicinal product for these applications is Destolit 150 mg tablets, which was first authorised to Aventis Pharma Limited (PL 04425/0045) on 09 July 1982. Following a change of ownership procedure on 04 December 1997, this Marketing Authorisation was transferred to Norgine Limited, UK (PL 00322/0076).

Ursodeoxycholic acid (UDCA) is a gallstone dissolving agent which acts by reducing the content of cholesterol in bile.

The Applicant submitted one pilot and one pivotal bioequivalence studies, comparing the pharmacokinetic profile of Ursodeoxycholic acid 4 x 150 mg tablets with Destolit 4 x 150 mg tablets of (Norgine Ltd, UK) in healthy, adult, male, volunteers in the fed state. This study was performed in compliance with Good Clinical Practice.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of these products.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The member states considered that the applications could be approved at the end of procedure (Day 210) on 02 March 2018. After a subsequent national phase, marketing authorisations (PL 00289/2169-2170) were granted in the UK on 28 March 2018.

## II QUALITY ASPECTS

### II.1 Introduction

The finished products are presented as tablets. Each tablet contains 300 mg or 500 mg ursodeoxycholic acid, as the active ingredient. Other ingredients consist of the pharmaceutical excipients lactose monohydrate, pregelatinised maize starch, sodium starch glycolate, purified talc, magnesium stearate and purified water.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of purified talc which complies with British Pharmacopoeia (BP). Satisfactory batch analysis data and Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as required for human consumption. Confirmation has also been given that the magnesium stearate used in the tablets is of vegetable origin.

These products do not contain or consist of genetically modified organisms (GMO).

The finished products are packaged in polyvinylchloride (PVC)/aluminium blisters containing pack sizes of 60 or 100 tablets.

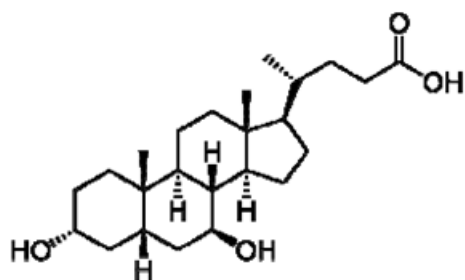
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

### II.2 Drug Substance

INN: Ursodeoxycholic acid

Structure:



Molecular formula: C<sub>24</sub>H<sub>40</sub>O<sub>4</sub>

Molecular weight: 392.6 g/mol

Description: White to almost white powder.

Solubility: Practically insoluble in water, freely soluble in ethanol, slightly soluble in acetone and practically insoluble in methylene chloride.

Ursodeoxycholic acid is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance, ursodeoxycholic acid, are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

### **II.3. Medicinal Product**

#### **Pharmaceutical Development**

The objective of the development programme was to formulate safe, efficacious tablets containing 300 mg and 500 mg ursodeoxycholic acid per tablet, that are alternative strengths compared to the reference product Destolit 150 mg tablets (Norgine Limited, UK). A satisfactory account of the pharmaceutical development has been provided.

The proposed strengths of Ursodeoxycholic acid 300 mg and 500 mg Tablets were developed by a proportional increase in the amount of active ingredient and excipients to that of the Ursodeoxycholic acid 150 mg Tablets authorised to Auden McKenzie Limited (PL 17507/0228).

Comparative *in vitro* dissolution has been provided between the proposed Ursodeoxycholic acid 300 mg Tablets, Ursodeoxycholic acid 500 mg Tablets and the existing in-house developed Ursodeoxycholic acid 150 mg Tablets (authorised to Auden McKenzie Limited).

Comparative impurity profiles have also been provided.

#### **Manufacture of the products**

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale batch size and has shown satisfactory results.

#### **Finished Product Specifications**

The finished product specifications proposed are acceptable. The test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

#### **Stability of the Products**

Finished product stability studies were performed in accordance with current guidelines on batches of the finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 2 years with no special storage conditions.

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

There are no objections to the approval of these applications from a pharmaceutical viewpoint.

### III NON-CLINICAL ASPECTS

#### III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of ursodeoxycholic acid are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

#### III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

#### III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

#### III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

#### III.5 Ecotoxicity/environmental risk assessment (ERA)

Since Ursodeoxycholic acid Tablets are intended for use in place of existing products, this will not lead to an increase of the environmental exposure. An environmental risk assessment is therefore not deemed necessary.

#### III.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being 'hybrid' medicinal products of an originator product that has been licensed for over 10 years.

There are no objections to the approval of these applications from a non-clinical viewpoint.

### IV CLINICAL ASPECTS

#### IV.1 Introduction

The clinical pharmacology of ursodeoxycholic acid is well-known. With the exception of data from the bioequivalence studies (pilot and pivotal studies) detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for these applications.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of ursodeoxycholic acid.

Based on the data provided, Ursodeoxycholic acid 4 x 150 mg Tablets can be considered bioequivalent to Destolit 4 x 150 mg tablets (Norgine Ltd, UK). Satisfactory justification for the use of a 600 mg dose has been provided.

#### IV.2 Pharmacokinetics

In support of these applications, the applicant submitted the following bioequivalence studies:

##### **Pilot Study**

**An open label, balanced, randomised, two-treatment, two-sequence, two-period crossover, pilot study to compare and evaluate single-dose pharmacokinetic profile of Ursodeoxycholic acid 4 x 150 mg tablets with Destolit 4 x 150 mg tablets (Norgine Ltd, U.K.) in healthy, adult, male, human subjects in a fed state.**

The aim was to compare the rate and extent of absorption of a single-dose of the test product with the reference product under fed conditions to obtain an estimate of the variability of the primary PK indices  $C_{max}$  and  $AUC_{0-72h}$  to calculate a sample size for a bioequivalence study and to evaluate the safety and tolerability of a single 4 x 150 mg dose of Ursodeoxycholic acid Tablets.

Subjects were fasted overnight for at least 10 hours before a high-fat breakfast on the two days from admission in each study period (Days -2 and -1) and on each dosing day until 4 hours afterwards. Standardised identical meals were provided at approximately 4, 8, 12, and 24 hours after dosing in each period.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 30 days.

The statistical plan is well described. There have been no serious or clinically significant protocol deviations.

## Results

### Unconjugated UDCA

Geometric Least Squares Means, Ratios and 90% Confidence Interval for Pharmacokinetic Parameters ( $C_{max}$  and  $AUC_{0-72h}$ ) of baseline-corrected Unconjugated Ursodiol (N=14)

Pharmacokinetic Parameter	Ln-trnasformed			90% Confidence Interval	
	Geometric Least Squares Means			Lower	Upper
	Test (T)	Reference (R)	T/R (%)		
$C_{max}$ (ng/ml)	5704.67	6423.21	88.81	77.16	102.22
$AUC_{0-72h}$ (ng.h/ml)	30896.05	32769.51	94.28	80.38	110.60

### Total UDCA

Geometric Least Squares Means, Ratios and 90% Confidence Interval for Pharmacokinetic Prameters ( $C_{max}$  and  $AUC_{0-72h}$ ) of baseline-corrected total Ursodiol (N=14)

Pharmacokinetic Parameter	Ln-trnasformed			90% Confidence Interval	
	Geometric Least Squares Means			Lower	Upper
	Test (T)	Reference (R)	T/R (%)		
$C_{max}$ (ng/ml)	9930.70	10333.96	96.10	84.17	109.72
$AUC_{0-72h}$ (ng.h/ml)	105229.38	119559.47	88.01	75.99	101.94

This pilot study allowed the Marketing Authorisation holder (MAH) to perform the sample size calculation and estimate power for their pivotal bioequivalence study. Results showed that equivalence was seen for AUC but not for  $C_{max}$  for unconjugated ursodiol and the other way round for total ursodiol. Intra-subject variability was seen to be moderate.

### Pivotal Study

This was a single-blind, balanced, randomised, two period, two sequence, single dose, crossover, oral, fed bioequivalence study of Ursodeoxycholic acid 4 x150 mg tablets with Destolit 4 x150 mg tablets (Norgine Limited, UK) in healthy, adult, males under fed conditions.

Following a standard screening assessment, volunteers were admitted to the study. In each period after 30 minutes of the start of a high fat high calorie breakfast, a single oral dose of 4 x UDCA 150 mg tablets of either test product (T) or reference product (R) was administered to sitting subjects according to a randomization schedule. Subjects remained upright for 4 hours after each drug administration except while undergoing venesection and medical examination.

Subjects were fasted overnight for at least 10 hours before a high-fat breakfast on the two days from admission in each study period (Days -2 and -1) and on each dosing day until 4 hours afterwards. Standardised identical meals were provided at approximately 4, 8, 12, and 24 hours after dosing in each period.

Blood samples were collected for plasma levels before dosing and up to and including 72 hours after each administration. The washout period between the treatment phases was 30 days.

The study design is a replicate of the pilot study, except that the sample size has been adjusted, based on the data from the pilot study.

The statistical analysis is acceptable.

## Results

### Unconjugated UDCA

Geometric Least Squares Means, Ratios and 90% Confidence Interval for Pharmacokinetic Parameters ( $C_{max}$  and  $AUC_{0-72h}$ ) of Unconjugated Ursodiol (N=58)

Pharmacokinetic Parameter	Ln-trnasformed			90% Confidence Interval	
	Geometric Least Squares Means			Lower	Upper
	Test (T)	Reference (R)	T/R (%)		
$C_{max}$ (ng/ml)	5390.82	5812.61	92.7	86.30	99.66
$AUC_{0-72h}$ (ng.h/ml)	32926.64	31437.26	104.7	97.90	112.06

### Total UDCA

Geometric Least Squares Means, Ratios and 90% Confidence Interval for Pharmacokinetic Parameters ( $C_{max}$  and  $AUC_{0-72h}$ ) of total Ursodiol (N=58)

Pharmacokinetic Parameter	Ln-trnasformed			90% Confidence Interval	
	Geometric Least Squares Means			Lower	Upper
	Test (T)	Reference (R)	T/R (%)		
$C_{max}$ (ng/ml)	7996.494	8559.588	93.4	87.36	99.90
$AUC_{0-72h}$ (ng.h/ml)	122504.613	117076.628	104.6	98.58	111.07

The 90% confidence intervals for  $C_{max}$  and  $AUC_{0-72h}$  were within the pre-defined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/ Corr\*\*). Bioequivalence has been shown for the test formulation (Ursodeoxycholic acid 4 x 150 mg tablets) and the reference formulation, Destolit 4 x 150 mg tablets of (Norgine Ltd, UK) in healthy, adult, male, human subjects in the fed state.

A biowaver was requested for the 300 mg and 500 mg strengths. Although the bioequivalence was demonstrated at the 150 mg strength following a pivotal bioequivalence study at 4 x150 mg, i.e., 600 mg

in total, justification for this was required. The applicant provided further explanation in response to this point. The qualitative composition of the different strengths is the same and the composition of the strengths is quantitatively proportional, including the excipients, both of which are reflected in the *in vitro* dissolution data. Regarding the pharmacokinetic (PK) linearity, it was acknowledged that the bibliographic data relating to UDCA PK is limited; although several references have suggested some degree of non-linear pharmacokinetics, the extent of which is unclear. However, based on the additional data, ursodeoxycholic acid seems to have a PK linearity from the 300 mg to 600 mg dose range and the difference in dose-adjusted AUC have met the criterion of  $\pm 25\%$ .

In the applicant's pivotal bioequivalence study, the AUC point estimates are close to 1 and it is therefore considered unlikely that results from the pivotal study with the 600 mg dose would have been shifted to such an extent that a different bioequivalence conclusion would have to be drawn for the 300 mg or the 500 mg dose. Therefore, the requested biowaiver can be accepted; no further bioequivalence studies are required.

### IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for applications of this type.

### IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for applications of this type.

### IV.5 Clinical safety

No new safety data were submitted and none were required for these applications.

### IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

The marketing authorisation holder has submitted an RMP, 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 Ursodeoxycholic acid 300 mg and 500 mg Tablets.

A summary of safety concerns, as approved in the RMP, are listed below:

<b>List of important risks and missing information</b>	
<b>Important identified risks</b>	<ul style="list-style-type: none"> <li>• Hepatic decompensation in primary biliary cirrhosis</li> <li>• Diarrhea</li> <li>• Biliary colic</li> <li>• Hypersensitivity and skin reactions</li> </ul>
<b>Important potential risks</b>	<ul style="list-style-type: none"> <li>• Teratogenicity</li> </ul>
<b>Missing information</b>	<ul style="list-style-type: none"> <li>• Off label use in patients with radio-opaque calcified gallstones, occlusion of biliary tract, frequent episodes of biliary colic and impaired contractility of gall bladder</li> <li>• Off label use in patients with acute inflammation of the gall bladder or biliary tract</li> <li>• Safety in breast feeding</li> </ul>

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

### IV.7 Discussion on the clinical aspects

The grant of marketing authorisations is recommended for these applications.

**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 language used for the purpose of user testing the package leaflet was English.

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*.

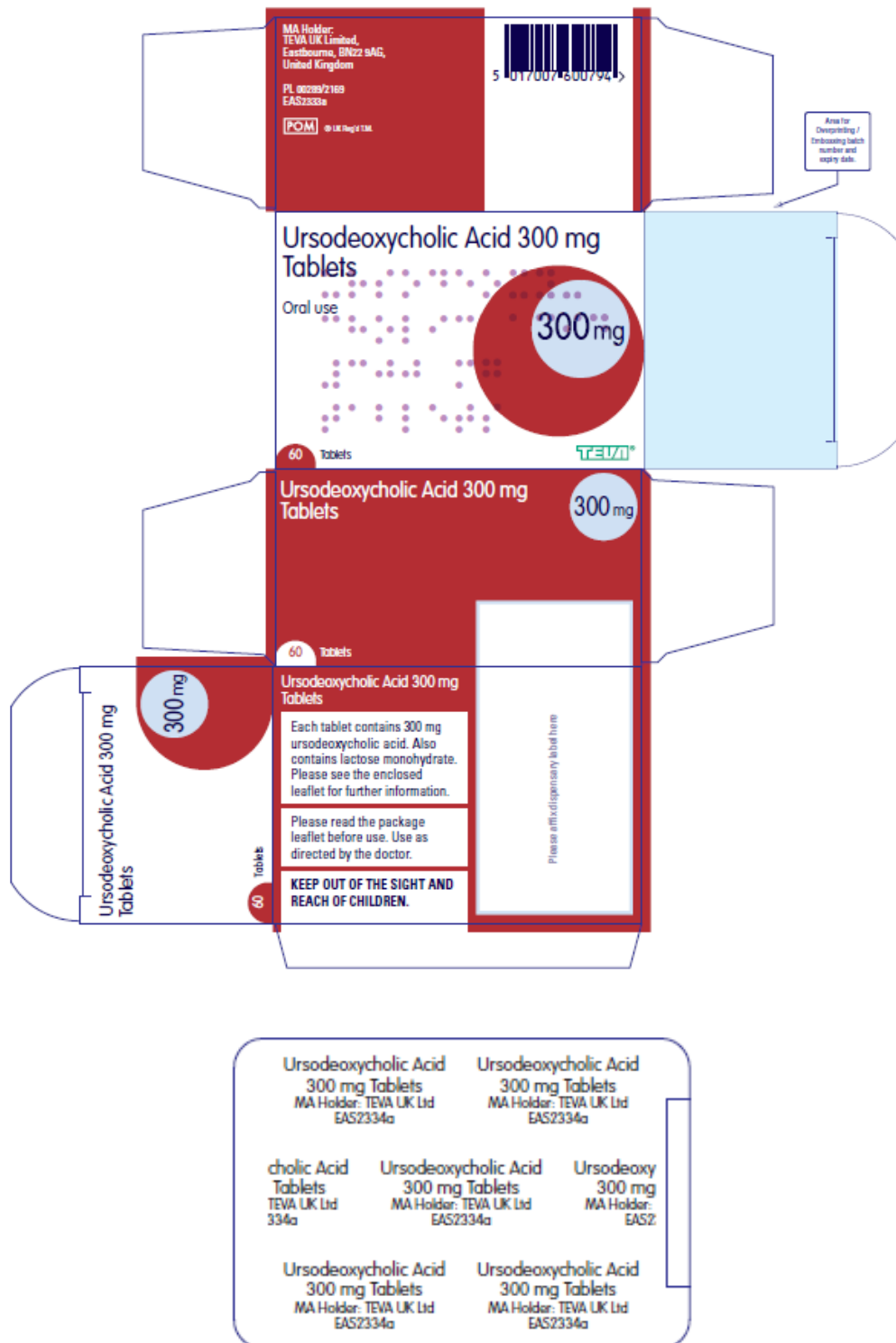
**VI Overall conclusion, benefit/risk assessment and recommendation**

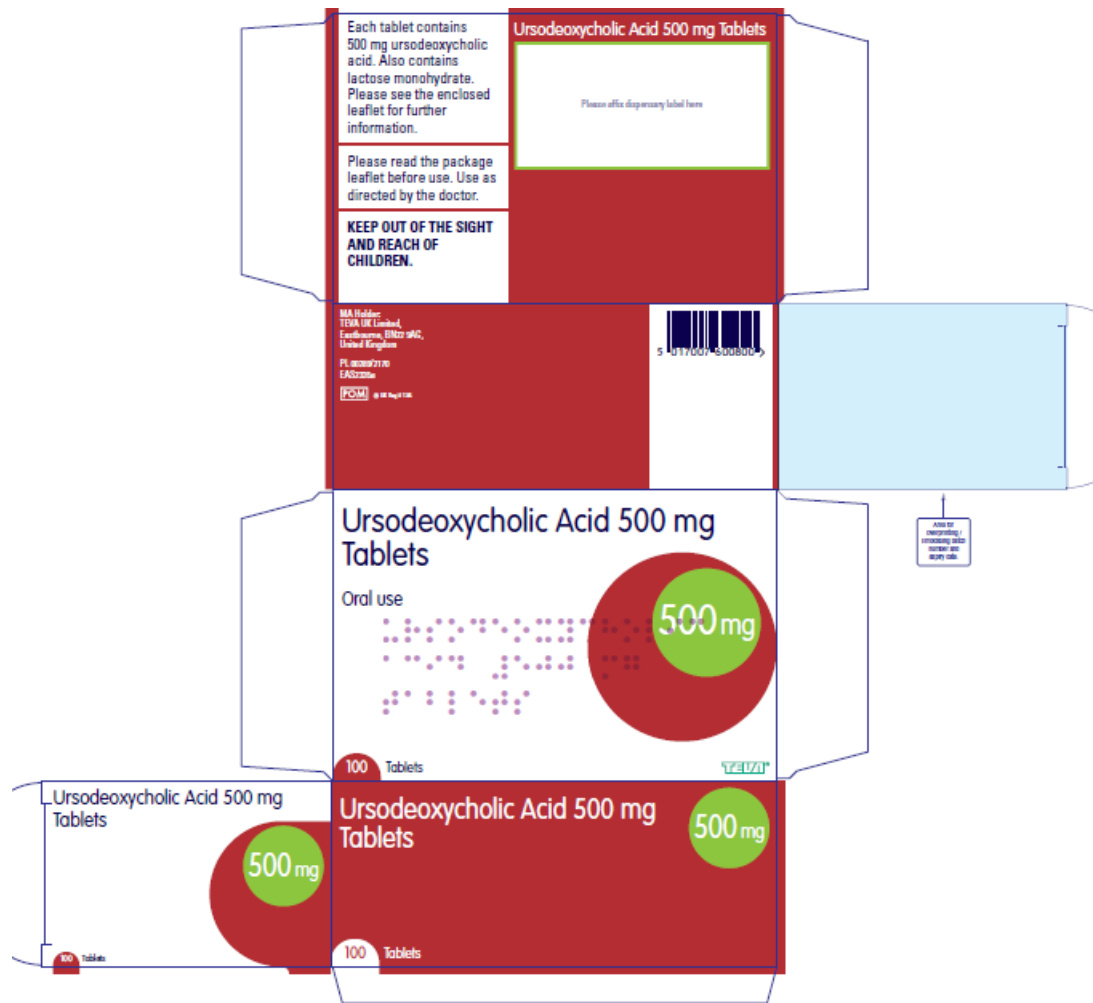
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Bioequivalence has been demonstrated between the applicant's product and the reference product. The benefit-risk assessment is, therefore, considered to be positive.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Ursodeoxycholic acid 300 mg and 500 mg Tablets is presented below:





Ursodeoxycholic Acid 500 mg Tablets MA Holder: TEVA UK Ltd EAS2336a	Ursodeoxycholic Acid 500 mg Tablets MA Holder: TEVA UK Ltd EAS2336a	Ursodeoxycholic Acid 500 mg Tablets MA Holder: TEVA UK Ltd EAS2336a	
Ursodeoxycholic Acid 500 mg Tablets TEVA UK Ltd 336a	Ursodeoxycholic Acid 500 mg Tablets MA Holder: TEVA UK Ltd EAS2336a	Ursodeoxycholic Acid 500 mg Tablets MA Holder: TEVA UK Ltd EAS2336a	Ursodeoxy 500 mg MA Holder: EAS2
Ursodeoxycholic Acid 500 mg Tablets MA Holder: TEVA UK Ltd EAS2336a	Ursodeoxycholic Acid 500 mg Tablets MA Holder: TEVA UK Ltd EAS2336a	Ursodeoxycholic Acid 500 mg Tablets MA Holder: TEVA UK Ltd EAS2336a	

## Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)