Public Assessment Report

Decentralised Procedure

URSODEOXYCHOLIC ACID 150MG TABLETS
(Ursodeoxycholic acid)

Procedure No: UK/H/4693/001/DC

UK Licence No: PL 17507/0228

Auden Mckenzie (Pharma Division) Ltd
This is a summary of the public assessment report (PAR) for Ursodeoxycholic Acid 150 mg Tablets (PL 17507/0228). It explains how Ursodeoxycholic Acid 150 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 150 mg Tablets.

For practical information about Ursodeoxycholic Acid 150 mg Tablets, patients should read the package leaflet or contact their doctor or pharmacist.

What are Ursodeoxycholic Acid 150 mg Tablets and what are they used for?

Ursodeoxycholic Acid 150 mg Tablets are a ‘generic medicine’. This means that Ursodeoxycholic Acid 150 mg Tablets are similar to a ‘reference medicine’ already authorised in the European Union (EU) called Destolit 150 mg Tablets (Norgine Limited).

Ursodeoxycholic Acid 150 mg Tablets are prescribed to help dissolve gallstones that are made mainly consist of cholesterol. The active ingredient in this medicine is ursodeoxycholic acid.

How are Ursodeoxycholic Acid 150 mg Tablets used?

This medicine can only be obtained with a prescription. The usual dose prescribed of Ursodeoxycholic Acid 150 mg Tablets is between 3 and 4 tablets a day, usually divided up and taken twice a day (i.e. 1 or 2 tablets taken with water after meals; one dose always taken after an evening meal). This medicine will work best if taken together with a low-cholesterol and calorie-controlled diet.

How do Ursodeoxycholic Acid 150 mg Tablets work?

Ursodeoxycholic acid is a chemical present naturally in the body and it helps to control the amount of cholesterol in the blood. This medicine helps dissolve gallstones that are made mainly of cholesterol.

How have Ursodeoxycholic Acid 150 mg Tablets been studied?

Ursodeoxycholic Acid 150 mg Tablets are a generic medicine; therefore, studies in patients have been limited to tests to determine that this medicine is bioequivalent to the reference medicine, Destolit 150 mg Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Ursodeoxycholic Acid 150 mg Tablets?

Ursodeoxycholic Acid 150 mg Tablets are a generic medicine that is bioequivalent to the reference medicine Destolit 150 mg Tablets. Therefore, the benefits and risks are taken as being the same as those of the reference medicine.

Why are Ursodeoxycholic Acid 150 mg Tablets approved?

It was concluded that, in accordance with EU requirements, Ursodeoxycholic Acid 150 mg Tablets have been shown to have comparable quality and to be bioequivalent to the reference medicine. Therefore, the view was that, as for the reference medicine, the benefit outweighs the identified risk.

What measures are being taken to ensure the safe and effective use of Ursodeoxycholic Acid 150
mg Tablets?

A risk management plan has been developed to ensure that Ursodeoxycholic Acid 150 mg Tablets is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Ursodeoxycholic Acid 150 mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Ursodeoxycholic Acid 150 mg Tablets

Ireland and the United Kingdom agreed to grant a Marketing Authorisation for Ursodeoxycholic Acid 150 mg Tablets on 29 April 2014. A Marketing Authorisation was granted in the UK on 28 May 2014.

The full PAR for Ursodeoxycholic Acid 150 mg Tablets follows this summary. For more information about treatment with Ursodeoxycholic Acid 150 mg Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in July 2014.
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# Module 1
## Information about initial procedure

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Ursodeoxycholic Acid 150 mg Tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10(1)</td>
</tr>
<tr>
<td><strong>Active Substances</strong></td>
<td>Ursodeoxycholic acid</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Tablets</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>150 mg</td>
</tr>
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</table>
| **MA Holder** | Auden Mckenzie (Pharma Division) Ltd  
McKenzie House  
Bury Street  
Ruislip  
Middlesex  
HA4 7TL  
UK |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Ireland |
| **Procedure Number** | UK/H/4693/001/DC |
| **Timetable** | Day 210 – 29 April 2014 |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summary of Product Characteristics (SmPC) for products that have been granted Marketing Authorisations at a national level is available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflet for products that are granted Marketing Authorisations at a national level is available on the MHRA website.
Module 4
Labelling
Module 5
Scientific discussion during initial procedure

I   INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Ursodeoxycholic Acid 150 mg Tablets (PL 17507/0228; UK/H/4693/001/DC) could be approved. This application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Ireland as Concerned Member States (CMS).

This product can only be obtained with a prescription (legal classification POM).

This application was made under the Decentralised Procedure (DCP), according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of the reference product, Destolit 150 mg Tablets. Destolit 150 mg Tablets were originally granted a marketing authorisation to Aventis Pharma Limited on 09 July 1982 (PL 04425/0045). Following a change of ownership, granted on 04 December 1997, the current Marketing Authorisation Holder is Norgine Limited (PL 00322/0076).

Ursodeoxycholic Acid 150 mg Tablets contain the active substance ursodeoxycholic acid. Ursodeoxycholic acid is a gallstone dissolving agent, which acts by reducing the content of cholesterol in bile. This may be due either to a reduction in hepatic cholesterol synthesis or reduced absorption of cholesterol or both.

No new non-clinical studies were conducted, which is acceptable given that this application was based on being a generic medicinal product of the reference product, which has been licensed for over 10 years.

With the exception of the two pharmacokinetic studies comparing this product with that of the reference product, Destolit 150 mg Tablets (Norgine Ltd, UK), no new clinical studies were conducted. This is acceptable given that this application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years. The pilot and bioequivalence studies were carried out in accordance with Good Clinical Practice (GCP).

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

The RMS and CMS considered that the application could be approved at the end of procedure on 29 April 2014. After a subsequent national phase, a marketing authorisation was granted in the UK on 28 May 2014.
II ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Ursodeoxycholic Acid 150 mg Tablets</th>
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</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Ursodeoxycholic acid</td>
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<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Bile acid preparations (A05AA02)</td>
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<td>Pharmaceutical form and strength(s)</td>
<td>Tablets 150 mg</td>
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<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/4693/001/DC</td>
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<td>Reference Member State</td>
<td>UK</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Ireland</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 17507/0228</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Auden Mckenzie (Pharma Division) Ltd McKenzie House Bury Street Ruislip Middlesex HA4 7TL UK</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance – Ursodeoxycholic acid

rINN: Ursodeoxycholic acid

Chemical name: 3α, 7β-dihydroxy-5β-cholan-24-oic acid

Structure:

\[\text{Molecular formula: } C_{24}H_{40}O_4\]

\[\text{Molecular weight: } 392.56 \text{ g/mol}\]

Appearance: A white or almost white powder.

Solubility: Practically insoluble in water, freely soluble in ethanol (96 percent), slightly soluble in acetone, 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. Further, a TSE certificate of suitability has been provided for the manufacture of ursodeoxycholic acid to show that it is manufactured in line with current guidelines concerning the minimisation of TSE/BSE (Transmissible Spongiform Encephalopathies/Bovine Spongiform Encephalopathy).

Satisfactory specifications have been provided for all packaging used for storing the active substance ursodeoxycholic acid. The primary packaging has been shown to comply with current legislation concerning materials in contact with foodstuff.

Appropriate stability data have been generated showing the active substance to be physically and chemically stable. A suitable retest period has been set based on stability data submitted for the active substance when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the following pharmaceutical excipients lactose monohydrate, pregelatinised maize starch, sodium starch glycolate, talc and magnesium stearate.

All excipients used comply with their respective European Pharmacopoeia monographs.

With the exception of lactose monohydrate, none of the excipients are of animal or human origin. The supplier of lactose monohydrate has confirmed that it is sourced from healthy animals under the same conditions as milk for human consumption. Magnesium stearate, which can be derived from animals, was sourced from vegetable oil. No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The objective of the development programme was to formulate a globally acceptable, stable and bioequivalent product containing ursodeoxycholic acid that could be considered a generic medicinal product of the reference product Destolit 150 mg Tablets (Norgine Ltd, UK).
Comparative physico-chemical data, including *in vitro* dissolution and impurity profiles have been provided for the proposed product versus the reference product, and pharmaceutical equivalence has been shown.

A satisfactory account of the pharmaceutical development has been provided.

**Manufacturing Process**
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product.

Process validation has been carried out on three full scale commercial-scale batches of finished product. The results are satisfactory.

**Finished Product Specification**
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

**Container-Closure System**
The finished product is packaged in aluminium/polyvinylchloride blister packs of 60 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

**Stability of the product**
Stability studies were performed, in accordance with current guidelines, on batches of finished product manufactured by the finished product manufacturer and packed in the packaging proposed for marketing. The results from these studies support a shelf-life of 2 years. Ursodeoxycholic Acid 150 mg Tablets do not have any special storage conditions.

**Bioequivalence/bioavailability**
Two pharmacokinetic studies were performed comparing the test product Ursodeoxycholic Acid 150 mg Tablets (Auden Mckenzie Limited, UK) versus the reference product Destolit 150 mg Tablets (Norgine Ltd, UK). Suitable certificates of analysis have been provided for the test and reference products used in both studies.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPC, PIL and labels are acceptable from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (“user testing”), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Marketing Authorisation Application (MAA) form**
The MAA form is satisfactory from a pharmaceutical perspective.

**Quality Overall Summary (Expert report)**
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable
summary of the pharmaceutical dossier.

**Conclusion**
The grant of a Marketing Authorisation is recommended.

### III.2 NON-CLINICAL ASPECTS

As the pharmacodynamic, pharmacokinetic and toxicological properties of ursodeoxycholic acid are well-known, no further non-clinical studies are required and none have been provided.

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

Suitable justification has been provided for the non-submission of an environmental risk assessment. As this product is intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

There are no objections to the approval of this product from a non-clinical viewpoint.

### III.3 CLINICAL ASPECTS

**Pharmacokinetics and Pharmacodynamics**

With the exception of the following studies, no new pharmacodynamic or pharmacokinetic data have been submitted with this application and none are required.

In support of this application, the Marketing Authorisation Holder has submitted one bioequivalence study and one pilot study.

1. The following pilot study was submitted:

   **An open-label, randomised, balanced, two-treatment, two-sequence, two-period crossover, pilot study to compare and evaluate the single-dose pharmacokinetic profiles of the test product Ursodeoxycholic acid 4 x 150 mg tablets (Auden McKenzie Limited, UK) versus the reference product Destolit 4 x 150 mg tablets (Norgine Ltd, UK) in healthy, adult, male, human subjects in a fed state**

   The aim of the pilot study was to obtain an estimate of the variability of the primary pharmacokinetic indices C$_{\text{max}}$ 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 150mg dose of the test product.

   Following an overnight fast of at least 10 hours, subjects were dosed orally after a period of 30 minutes of the start of a high-fat, high-calorie breakfast, with either the test or reference product. Blood samples were taken pre-dose and up to 72 hours post dose. There was a washout period of 30 days between each dosing period.
A summary of the main pilot study results is presented in the tables below:

Table 7: 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)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Ln-transformed Geometric Least Squares Means</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (T)</td>
<td>Reference (R)</td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>5704.67</td>
<td>6423.21</td>
</tr>
<tr>
<td>AUC_{0-72h} (ng·h/ml)</td>
<td>30895.05</td>
<td>32789.51</td>
</tr>
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</table>

Table 17: Geometric Least Squares Means, Ratios and 90% Confidence Interval for Pharmacokinetic Parameters (C_{max} and AUC_{0-72h}) of Baseline-corrected Total Ursodiol (N=14)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Ln-transformed Geometric Least Squares Mean</th>
<th>90% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Test (T)</td>
<td>Reference (R)</td>
</tr>
<tr>
<td>C_{max} (ng/ml)</td>
<td>9930.70</td>
<td>10333.96</td>
</tr>
<tr>
<td>AUC_{0-72h} (ng·h/ml)</td>
<td>105229.38</td>
<td>119559.47</td>
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</table>

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
Total Ursodiol (unconjugated plus glycine and taurine–conjugated)

The 90% confidence interval of the test/reference ratio for baseline-corrected unconjugated ursodiol for AUC_{0-t} was within the predefined limits of 80.00-125.00%, as specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). However, the 90% confidence interval of the test/reference ratio for C_{max} was not within the predefined limits.

The 90% confidence interval of the test/reference ratio for baseline-corrected total unconjugated ursodiol for C_{max} was within the predefined limits of 80.00-125.00%, as specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). However, the 90% confidence interval of the test/reference ratio for AUC_{0-t} was not within the predefined limits.

In conclusion, the pilot study allowed the Marketing Authorisation Holder to perform the sample size calculation and estimate power for their formal bioequivalence study. Intra-subject variability was seen to be moderate; however, this study is seen as an acceptable pilot to the main bioequivalence study.

2. The following bioequivalence study was submitted:

A single-blind, balanced, randomized, two-period, two-sequence, single-dose, crossover, oral, fed bioequivalence study of Ursodeoxycholic Acid 4 x 150 mg tablets from Auden Mckenzie (Pharma Division) Limited, UK with Destolit 4 x 150 mg tablets from Norgine Limited, UK in healthy, adult, males under fed conditions.
Following an overnight fast of at least 10 hours, healthy male subjects were dosed orally after a period of 30 minutes of the start of a high-fat, high-calorie breakfast, with a single 4 x 150mg dose of either the test or reference product. Blood samples were taken pre-dose and up to 72 hours post dose. There was a washout period of 30 days between each dosing period.

A summary of the main results is presented in the tables below:

### Table 24: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Pharmacokinetic Parameters $C_{max}$ and $AUC_{0-72h}$ of Unconjugated Ursodiol (N=58)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Ln-transformed</th>
<th>90% Confidence Interval T vs R (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric Least Squares Mean</td>
<td>Test Product (T)</td>
</tr>
<tr>
<td>$C_{max}$ (ng/ml)</td>
<td>5390.82</td>
<td>5812.61</td>
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<tr>
<td>$AUC_{0-72h}$ (ng.h/ml)</td>
<td>32926.64</td>
<td>31437.26</td>
</tr>
</tbody>
</table>

*All figures are rounded to two decimal places.

### Table 25: Geometric Least Squares Mean, Ratios and 90% Confidence Interval for Pharmacokinetic Parameters $C_{max}$ and $AUC_{0-72h}$ of Total Ursodiol (N=58)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters (Units)</th>
<th>Ln-transformed</th>
<th>90% Confidence Interval T vs R (Parametric)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Geometric Least Squares Mean</td>
<td>Test Product (T)</td>
</tr>
<tr>
<td>$C_{max}$ (ng/ml)</td>
<td>7996.494</td>
<td>8559.588</td>
</tr>
<tr>
<td>$AUC_{0-72h}$ (ng.h/ml)</td>
<td>122504.613</td>
<td>117076.628</td>
</tr>
</tbody>
</table>

*All figures are rounded to two decimal places.

$AUC_{0-1}$ area under the plasma concentration-time curve from time zero to t hours  
$C_{max}$ maximum plasma concentration  
Total Ursodiol (unconjugated plus glycine and taurine –conjugated)

The 90% confidence intervals of the test/reference ratio for baseline-corrected unconjugated and total unconjugated ursodiol for $AUC_{0-1}$ and $C_{max}$ were within the pre-defined limits of 80.00-125.00%, as specified in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**). In conclusion bioequivalence has been demonstrated between the test and reference products.

**Efficacy**
No new data on efficacy have been submitted and none are required for this type of application.

**Safety**
With the exception of the data generated during the pilot and bioequivalence studies, no new safety data were submitted and none were required. No new or unexpected safety issues arose from these studies.
SmPC, PIL and Labels
The SmPC, PIL and labels are acceptable from a clinical perspective.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A Risk Management Plan has been developed to ensure that Ursodeoxycholic Acid 150 mg Tablets are used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for Ursodeoxycholic Acid 150 mg Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Conclusion
The grant of a Marketing Authorisation is recommended.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Ursodeoxycholic Acid 150 mg Tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Ursodeoxycholic Acid 150 mg Tablets and the relevant reference product.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labels are satisfactory and consistent with those for the reference product.

BENEFIT-RISK ASSESSMENT
The quality of the product 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. Extensive clinical experience with ursodeoxycholic acid is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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