Public Assessment Report

UKPAR

Ursodeoxycholic acid 250mg Hard Capsules

(ursodeoxycholic acid)

UK Licence No: PL 13606/0201

Co-Pharma Limited
LAY SUMMARY
Ursodeoxycholic acid 250mg Hard Capsules
(ursodeoxycholic acid)

This is a summary of the Public Assessment Report (PAR) for Ursodeoxycholic acid 250mg Hard Capsules (PL 13606/0201). It explains how Ursodeoxycholic acid 250mg Hard Capsules 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 250mg Hard Capsules.

For practical information about using Ursodeoxycholic acid 250mg Hard Capsules, patients should read the package leaflet or contact their doctor or pharmacist.

What are Ursodeoxycholic acid 250mg Hard Capsules and what are they used for?
This medicine is the same as Ursodeoxycholic Acid 250mg Hard Capsules (PL 28176/0120), which is already authorised. The company that makes Ursodeoxycholic Acid 250mg Hard Capsules, Strides Arcolab International Limited, has agreed that its scientific data can be used as a basis for the grant of an identical licence for Ursodeoxycholic acid 250mg Hard Capsules (Co-Pharma Limited; PL 13606/0201).

Ursodeoxycholic acid is used:
- to dissolve gallstones caused by excess cholesterol in the gall bladder (in patients for whom surgery is not an option), where the gallstones are not visible on a plain x-ray (gallstones that are visible will not dissolve) and not more than 15 mm in diameter. The gall bladder should still be working despite the gallstone(s).

- for the treatment of a condition where the bile ducts in the liver become damaged leading to a build-up of bile. This may cause scarring of the liver. The liver should not be so damaged that it is not functioning properly. This condition is called primary biliary cirrhosis.

- for Paediatric population: to treat children, aged 6 years to less than 18 years, who have liver problems associated with cystic fibrosis.

How do Ursodeoxycholic acid 250mg Hard Capsules work?
Ursodeoxycholic acid 250mg Hard Capsules contain the active ingredient ursodeoxycholic acid, a chemical present naturally in the body that helps to control the amount of cholesterol in the blood.

How are Ursodeoxycholic acid 250mg Hard Capsules used?
The pharmaceutical form of this medicine is a capsule that is taken orally. The whole capsule should be swallowed with a drink of water or other liquid and must be taken regularly.

Primary Biliary Cirrhosis – (Stage I-III)
Use in patients with damage to liver tissue by impaired bile flow
The dose will be determined depending on patient’s body weight. During the first 3 months of treatment, patients should take 3-7 capsules in divided doses throughout the day. As the liver function improves, the total daily dose can be taken once, in the evening.
In patients with primary biliary cirrhosis, the symptoms may worsen at the start of treatment, for example the itching may increase. This only occurs in rare cases. If this happens, therapy can be continued with a lower daily dose of ursodeoxycholic acid. Each week, a doctor will then gradually increase the daily dose, until the required dose is reached.

**Use in patients with gallstones**
The recommended dose is approximately 10 mg ursodeoxycholic acid per kg body weight per day, taken as follows
It generally takes 6-24 months to dissolve gallstones. The duration of a treatment depends on the size of the existing gallstones at the beginning of the treatment. Patients should continue with the treatment even if the symptoms have disappeared. Stopping treatment may result in the extension of the total treatment time. After the gallstones have been dissolved, the treatment should be continued for 3-4 months. If there is no reduction in the size of the gallstones after 12 months, therapy should be stopped. Every 6 months, a doctor should check whether the treatment is working. At each of these follow-up examinations, it should be checked whether a build-up of calcium causing hardening of the stones has occurred since the last time. If this happens, a doctor will stop the treatment.

Use in Children
The dose in children with cystic fibrosis aged 6 years to less than 18 years is 20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary. There are no age limits to the use of Ursodeoxycholic acid 250mg hard capsules. The administration of Ursodeoxycholic acid is based on body weight and the medical condition. If the patient cannot swallow capsules or has a bodyweight below 47 kg, other pharmaceutical forms (suspension) are available.

Ursodeoxycholic acid 250mg Hard Capsules can be obtained on prescription from a doctor.

For further information on how Ursodeoxycholic acid 250mg Hard Capsules are used, refer to the Summary of Product Characteristics or the package leaflet available on the MHRA website.

What benefits of Ursodeoxycholic acid 250mg Hard Capsules have been shown in studies?
Ursodeoxycholic acid 250mg Hard Capsules (PL 13606/0201) are considered to be identical to the previously authorised product, Ursodeoxycholic Acid 250mg Hard Capsules (PL 28176/0120), with the same benefits and risks, so, no new studies have been provided for Ursodeoxycholic acid 250mg Hard Capsules but reference is made to the studies for Ursodeoxycholic Acid 250mg Hard Capsules (PL 28176/0120).

What are the possible side effects of Ursodeoxycholic acid 250mg Hard Capsules?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common side effects with Ursodeoxycholic acid 250mg Hard Capsules (which may affect up to 1 in 10 people) are soft, loose stools or diarrhoea. Patients should inform a doctor immediately if they have persistent diarrhoea, as this may require a reduction in the dose of the medicine. Patients who suffer from diarrhoea should ensure that they drink enough liquids to replace their fluid and salt balance.

For the full list of all side effects reported with Ursodeoxycholic acid 250mg Hard Capsules, see section 4 of the package leaflet. For the full list of restrictions, see the package leaflet.

Why were Ursodeoxycholic acid 250mg Hard Capsules approved?
No new or unexpected safety concerns arose from this application. The MHRA, therefore, considered that the benefits of Ursodeoxycholic acid 250mg Hard Capsules outweigh its risks; and the grant of a Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Ursodeoxycholic acid 250mg Hard Capsules?
A Risk Management Plan (RMP) has been developed to ensure that Ursodeoxycholic acid 250mg Hard Capsules are 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 250mg Hard Capsules 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 250mg Hard Capsules**
A Marketing Authorisation was granted in the UK on 20 November 2015.

The full PAR for Ursodeoxycholic acid 250mg Hard Capsules follows this summary.

For more information about treatment with Ursodeoxycholic acid 250mg Hard Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in December 2015.
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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) granted Co-Pharma Limited a Marketing Authorisation for the medicinal product Ursodeoxycholic acid 250mg Hard Capsules (PL 13606/0201) on 20 November 2015. This prescription only medicine (POM) is used to treat the following indications:

- Treatment of primary biliary cirrhosis (PBC) in patients without decompensated cirrhosis
- Dissolution of radiolucent cholesterol gallstones not larger than 15 mm in diameter in patients with a functioning gallbladder and for whom surgical treatment is not indicated
- Paediatric population: Hepatobiliary disorder associated with cystic fibrosis in children aged 6 years to less than 18 years.

This application was submitted as an abridged simple application, according to Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Ursodeoxycholic Acid 250mg Hard Capsules, which was first authorised to Strides Arcolab International Limited (PL 28176/0120) on 05 December 2013.

Bile acids are the most important components of bile and play a role in stimulating bile production. Bile acids are also important to keep cholesterol dissolved in bile. In healthy individuals, the ratio between cholesterol concentrations and bile acids in the gallbladder is such that cholesterol is kept dissolved for most of the day. Thus, no gallstones can form (bile is non-lithogenic). In patients with cholesterol stones in the gallbladder, this ratio has altered and the bile is supersaturated with cholesterol (bile is lithogenic). After some time, this may cause precipitation of cholesterol crystals and the formation of gallstones. Ursodeoxycholic acid can convert lithogenic bile into non-lithogenic bile and also gradually dissolve cholesterol gallstones.

No new data were submitted nor were they necessary for this simple application, as the data are identical to that of the previously granted cross-reference product.

The MHRA 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 and assembly of this product.

A summary of the pharmacovigilance system and a detailed risk management plan have been provided with this application and these are satisfactory.
II QUALITY ASPECTS

II.1 Introduction

This is a simple, informed consent application for Ursodeoxycholic acid 250mg Hard Capsules submitted under Article 10c of Directive 2001/83/EC, as amended. The applicant has cross-referred to Ursodeoxycholic Acid 250mg Hard Capsules, which was first authorised to Strides Arcolab International Limited (PL 28176/0120) on 05 December 2013. The application is considered valid.

II.2. Drug Substance

Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

II.3. Medicinal Product

Name
The proposed product name for this application is Ursodeoxycholic acid 250mg Hard Capsules. The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack size
Each hard gelatin capsule contains 250 mg ursodeoxycholic Acid. The route of administration is oral.

The finished product is packed in colourless polyvinylchloride (PVC) film with aluminium blister foil packed in cardboard cartons. Pack sizes of 20, 28, 30, 50, 56, 60, 100 and 120 capsules are available. Not all pack sizes may be marketed.

The proposed shelf-life is 3 years with no special storage conditions.

The proposed packaging and shelf-life are consistent with the details registered for the cross-reference product.

Legal status
This product is a Prescription Only Medicine (POM).

Marketing Authorisation Holder/Contact Persons/Company
Co-Pharma Limited, Unit 4, Metro Centre, Watford, Hertfordshire WD18 9SS, United Kingdom

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory Curriculum Vitae (CV) has been provided.

Manufacturer
The proposed manufacturing site is consistent with that registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

Manufacturing process
The proposed manufacturing process is consistent with the details registered for the cross-reference product and the maximum batch size is stated.
Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

TSE Compliance
None of the excipients contain materials of animal or human origin. This is consistent with the cross-reference product.

Bioequivalence
No bioequivalence data are required to support this simple abridged application as the proposed product is manufactured to the same formula utilising the same process as the cross-reference product, Ursodeoxycholic Acid 250mg Hard Capsules (PL 28176/0120).

Expert Report
The applicant cross-refers to the data for Ursodeoxycholic Acid 250mg Hard Capsules (PL 28176/0120), to which this application is claimed to be identical. This is acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The data submitted with the application are acceptable. The grant of a Marketing Authorisation is recommended.

III NON-CLINICAL ASPECTS
Introduction
As this is an abridged simple application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

Environmental Risk Assessment (ERA)
A suitable justification has been provided for not submitting an environmental risk assessment. As the application is an identical version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV CLINICAL ASPECTS
Introduction
As this is an abridged simple application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

Risk Management Plan (RMP)
The Marketing Authorisation Holder (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 Ursodeoxycholic acid 250mg Hard Capsules.
Summary of the safety concerns

| Important identified risks                                                                 | • Diarrhoea  
|                                                                                           | • Biliary colic  
|                                                                                           | • Decompensation of hepatic cirrhosis in patients with advanced stage of primary biliary cirrhosis  
|                                                                                           | • Hypersensitivity and skin reactions  
|                                                                                           | • Calcification of gallstones (when used for the dissolution of gall stones)  

| Important potential risks                                                                 | • Teratogenicity  
|                                                                                           | • 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 gall bladder  
|                                                                                           | • Off-label use in patients with acute inflammation of the gall bladder or biliary tract  
|                                                                                           | • Off-label use in children with biliary atresia following unsuccessful portoenterostomy or without recovery of good bile flow  

| Missing information                                                                      | • Safety in breastfeeding  

Summary of risk minimisation measures
Routine risk minimisation is provided through the summary of product characterisation and the patient information leaflet. No additional risk minimisation measures are planned for this product.

Discussion on the clinical aspects
The grant of a Marketing Authorisation is recommended for this application.

V USER CONSULTATION
User-testing of the patient information leaflet for Ursodeoxycholic Acid 250mg Hard Capsules (Co-Pharma Limited) has been accepted based on the bridging report provided by the applicant making reference to the successful user-testing of the PIL for Ursodeoxycholic Acid 250mg Hard Capsules (PL PL 28176/0120; Strides Arcolab International Limited) as the ‘parent PIL’.
VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The quality of the product is acceptable, and no new non-clinical or clinical concerns have been identified. The applicant’s product is identical to 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.
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 250mg Hard Capsules is presented below:
Ursodeoxycholic acid 250 mg Hard Capsules

For oral use only
Swallow whole with liquid

Ursodeoxycholic acid 250 mg Hard Capsules
30 Capsules

Each hard gelatin capsule contains Ursodeoxycholic acid 250 mg
Read the package leaflet before use.
Keep out of the sight and reach of children.
This medicinal product does not require any special storage conditions.
Medicinal product subject to medical prescription

Ursodeoxycholic acid 250 mg Hard Capsules
30 Capsules

Details to be overprinted
Ursodeoxycholic acid 250 mg Hard Capsules

For oral use only
Swallow whole with liquid

50 Capsules

Ursodeoxycholic acid
250 mg Hard Capsules

Ursodeoxycholic acid

For oral use only
Swallow whole with liquid

50 Capsules
Ursodeoxycholic acid 250mg Hard Capsules

Ursodeoxycholic acid 250mg Hard Capsules

For oral use only
Swallow whole with liquid

120 Capsules

Ursodeoxycholic acid 250 mg Hard Capsules

Each hard gelatin capsule contains
Ursodeoxycholic acid 250mg

Store the package and tablets below sea,
Keep out of the sight and reach of children.
This medicinal product does not require any special
storage conditions.
Not oral product subject to
medical prescription
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Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitment)

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