

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ursodeoxycholic acid Strides 250mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard gelatin capsule contains Ursodeoxycholic Acid 250 mg.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, hard

White hard gelatin capsules (size '0') containing a white to off white powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic 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: Hepatobiliar disorder associated with cystic fibrosis in children aged 6 years to less than 18 years

4.2 Posology and method of administration

There are no age restrictions on the use of Ursodeoxycholic acid Strides 250mg hard capsules. For patients weighing less than 47 kg or patients who are unable to swallow Ursodeoxycholic acid Strides 250mg hard capsules, other formulations are available (suspension).

The following daily dose is recommended for the various indications:

For treatment of primary biliary cirrhosis (PBC)

Stage I-III

The daily dose is dependent on body weight and ranges from 3 to 7 capsules (12-16 mg ursodeoxycholic acid per kg of body weight).

During the first 3 months of treatment, Ursodeoxycholic acid Strides 250mg hard capsules should be taken in divided doses throughout the day. If liver function improves, the total daily dose can be taken once daily in the evening.

Body weight (kg)	Daily dose (mg/kg body weight)	Ursodeoxycholic acid Strides 250mg hard capsules			
		<u>First 3 months</u>			Subsequently
		Morning	Afternoon	Evening	Evening (once daily)
47 – 62	12 – 16	1	1	1	3
63 – 78	13 – 16	1	1	2	4
79 – 93	13 – 16	1	2	2	5
94 – 109	14 – 16	2	2	2	6

More than 110	2	2	3	7
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Stage IV:

In combination with increased serum bilirubin levels ($> 40 \mu\text{g/L}$; conjugated), only half the normal dosage should initially be given (see dosage for stages I - III), (6 - 8 mg ursodeoxycholic acid per kg body weight per day, equivalent to about 2 to 3 Ursodeoxycholic acid Strides 250mg hard capsules).

Thereafter, liver function should be closely monitored for several weeks (once every 2 weeks for 6 weeks). If there is no deterioration in liver function (AP, ALAT, ASAT, gamma-GT, bilirubin) and if no increased pruritus occurs, the dosage can be increased further to the usual level. However, liver function should again be closely monitored for several weeks. Once again, if there is no deterioration in liver function, the patient can be maintained at the normal dosage over the long term.

Patients with primary biliary cirrhosis (stage IV) without increased serum bilirubin levels are allowed to receive the normal starting dose immediately (see dosage stages I - III).

However, close monitoring of liver function, as described above, is likewise applicable in such cases; treatment of primary biliary cirrhosis will need to be regularly assessed on the basis of liver (laboratory) values and clinical findings.

The capsules should be swallowed whole with some liquid. Care should be taken to ensure that they are taken regularly.

Dissolution of Gallstones:

Adults: Approx. 10mg ursodeoxycholic acid (UDCA) per kg body weight per day according to:

- up to 60 kg: 2 capsules
- 61-80 kg: 3 capsules
- 81-100 kg: 4 capsules
- above 100 kg: 5 capsules

The capsules should be swallowed whole with some liquid in the evening before bedtime. Care should be taken to ensure that they are taken regularly.

Based on experience to date, the duration of the dissolution process with Ursodeoxycholic acid is 6 months to 2 years, depending on the initial size of the stones. For a proper assessment of the therapeutic outcome, it is necessary, at the start of treatment, to accurately determine the size of the existing stones and subsequently to monitor them regularly, for example, every 3 to 4 months, via new X-rays and/or ultrasound scans.

In patients whose stones have not decreased in size after six months of treatment at the dosage stated, it is recommended that the biliary lithogenic index be determined via duodenal samples. If the bile has an index of > 1.0 , it is unlikely that a favourable result can be obtained and it is better to consider a different form of treatment for gallstones. Treatment must be continued for 3 to 4 months after ultrasound follow-up has confirmed complete dissolution of the gallstones. Discontinuation of treatment for 3-4 weeks leads to a return of bile supersaturation and prolongs the overall duration of therapy. Discontinuation of treatment upon dissolution of the gallstones may be followed by a relapse.

Older people: There is no evidence to suggest that any alteration in the adult dose is needed but the relevant precautions should be taken into account.

Paediatric population: Children with cystic fibrosis aged 6 years to less than 18 years: 20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary

4.3 Contraindications

Ursodeoxycholic acid Strides 250mg hard capsules should not be used in patients with:

- Acute inflammation of the gall bladder or biliary tract
- occlusion of the biliary tract (occlusion of the common bile duct or a cystic duct)
- frequent episodes of biliary colic
- radio-opaque calcified gallstones
- impaired contractility of the gall bladder
- hypersensitivity to active substance or any excipients listed in section 6.1.
- Paediatric population: Unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia

4.4 Special warnings and precautions for use

Ursodeoxycholic acid Strides 250mg hard capsules should be taken under medical supervision.

During the first 3 months of treatment, liver function parameters AST (SGOT), ALT (SGPT) and γ -GT should be monitored by the physician every 4 weeks, thereafter every 3 months. Apart from allowing for identification of responders and non-responders in patients being treated for primary biliary cirrhosis, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advanced stage primary biliary cirrhosis.

When used for dissolution of cholesterol gallstones:

In order to assess therapeutic progress and for timely detection of any calcification of the gallstones, depending on stone size, the gall bladder should be visualised (oral cholecystography) with overview and occlusion views in standing and supine positions (ultrasound control) 6-10 months after the beginning of treatment.

If the gall bladder cannot be visualised on X-ray images, or in cases of calcified gallstones, impaired contractility of the gall bladder or frequent episodes of biliary colic, Ursodeoxycholic acid Strides 250mg hard capsules should not be used.

When used for treatment of advanced stage of primary biliary cirrhosis:

In very rare cases decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.

If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

Ursodeoxycholic acid Strides 250mg hard capsules should not be administered concomitantly with colestyramine, colestipol or antacids containing aluminium hydroxide and/or smectite (aluminium oxide), because these preparations bind ursodeoxycholic acid in the intestine and thereby inhibit its absorption and efficacy. Should the use of a preparation containing one of these substances be necessary, it must be taken at least 2 hours before or after Ursodeoxycholic acid Strides 250mg hard capsules.

Ursodeoxycholic acid Strides 250mg hard capsules can increase the absorption of ciclosporin from the intestine. In patients receiving ciclosporin treatment, blood concentrations of this substance should therefore be checked by the physician and the ciclosporin dose adjusted if necessary.

In isolated cases Ursodeoxycholic acid Strides 250mg hard capsules can reduce the absorption of ciprofloxacin.

Ursodeoxycholic acid has been shown to reduce the plasma peak concentrations (C_{max}) and the area under the curve (AUC) of the calcium antagonist nitrendipine.

An interaction with a reduction of the therapeutic effect of dapsone was also reported.

These observations together with in vitro findings could indicate a potential for ursodeoxycholic acid to induce cytochrome P450 3A enzymes. Controlled clinical trials have shown, however, that ursodeoxycholic acid does not have a relevant induction effect on cytochrome P450 3A enzymes.

Oestrogenic hormones and blood cholesterol lowering agents such as clofibrate may increase biliary lithiasis, which is a counter-effect to ursodeoxycholic acid used for dissolution of gallstones.

4.6 Fertility, pregnancy and lactation

There are no adequate data on the use of ursodeoxycholic acid, particularly in the first trimester of pregnancy. Animal studies have provided evidence of a teratogenic effect during the early phase of gestation (see section 5.3, Toxicity to reproduction). Ursodeoxycholic acid Strides 250mg hard capsules must not be used during pregnancy unless clearly necessary. Women of childbearing potential should be treated only if they use reliable contraception: non-hormonal or low-oestrogen oral contraceptive measures are recommended. However, in patients taking Ursodeoxycholic acid Strides 250mg hard capsules for dissolution of gallstones, effective non-hormonal contraception should be used, since hormonal oral contraceptives may increase biliary lithiasis.

The possibility of a pregnancy must be excluded before beginning treatment.

It is not known whether ursodeoxycholic acid passes into breast milk. Therefore, Ursodeoxycholic acid Strides 250mg hard capsules should not be taken during lactation. If treatment with Ursodeoxycholic acid Strides 250mg hard capsules is necessary, the infant should be weaned.

4.7 Effects on ability to drive and use machines

Ursodeoxycholic acid Strides has no influence on ability to drive and use machines .

4.8 Undesirable effects

The evaluation of undesirable effects is based on the following frequency data:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ to $< 1/1,000$)

Very rare / Not known ($< 1/10,000$ /cannot be estimated from available data)

Gastrointestinal disorders:

Common: pasty stools or diarrhoea (reported from clinical trials).

Very rare: severe right upper abdominal pain (during the treatment of primary biliary cirrhosis).

Frequency not known: vomiting.

Hepatobiliary disorders:

Very rare: calcification of gallstones, decompensation of hepatic cirrhosis(during therapy of the advanced stages of primary biliary cirrhosis), which partially regressed after the treatment was discontinued.

Frequency not known: increase of the serologic levels of alkaline phosphatase, γ -GT and bilirubin (in patients with an advanced stage of PBC).

Skin and subcutaneous disorders:

Very rare: urticaria.

Not Known: an exacerbation of pruritus (upon the beginning of UDCA administration in patients with cirrhosis).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Diarrhoea may occur in cases of overdose. In general, other symptoms of overdose are unlikely because the absorption of ursodeoxycholic acid decreases with increasing dose and therefore more is excreted with the faeces.

No specific counter-measures are necessary and the consequences of diarrhoea should be treated symptomatically with restoration of fluid and electrolyte balance.

5 PHARMACOLOGICAL PROPERTIES**5.1 Pharmacodynamic properties**

ATC Code: A05AA02, Bile Acid Preparations

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.

Studies into the effect of ursodeoxycholic acid on cholestasis in patients with impaired biliary drainage and on clinical symptoms in patients with biliary cirrhosis have shown a rapid decline in cholestatic symptoms in the blood (as measured by increased levels of alkaline phosphatase (AP), gamma-GT and bilirubin) and pruritus, as well as decreased fatigue in most patients.

Paediatric population

Cystic fibrosis

From clinical reports long-term experience up to 10 years and more is available with UDCA treatment in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepatobiliary changes if given at early stage of CFAHD.

Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made in order to optimize treatment effectiveness.

5.2 Pharmacokinetic properties

Ursodeoxycholic acid occurs naturally in the body. When given orally it is rapidly and completely absorbed. It is 96-98% bound to plasma proteins and efficiently extracted by the liver and excreted in the bile as glycine and taurine conjugates. In the intestine some of the conjugates are deconjugated and reabsorbed. The conjugates may also be dehydroxylated to lithocholic acid, part of which is absorbed, sulphated by the liver and excreted via the biliary tract.

5.3 Preclinical safety data

a) Acute toxicity

Acute toxicity studies in animals have not revealed any toxic damage.

b) Chronic toxicity

Subchronic toxicity studies in monkeys showed hepatotoxic effects in the groups given high doses, including functional changes (e.g. liver enzyme changes) and morphological changes such as bile duct proliferation, portal inflammatory foci and hepatocellular necrosis. These toxic effects are most likely attributable to lithocholic acid, a metabolite of ursodeoxycholic acid, which in monkeys – unlike humans – is not detoxified. Clinical experience confirms that the described hepatotoxic effects are of no apparent relevance in humans.

c) Carcinogenic and mutagenic potential

At doses 3.2 times the recommended maximum human dose, based on body surface area, UDCA produced an increased incidence of pheochromocytomas of the adrenal medulla in female rats in a life-span (2.5 year) study. Two-year studies in mice and rats revealed no evidence of carcinogenic potential. A tumour-promoting effect of the metabolite Lithocholic acid was observed when it was coadministered with a carcinogenic agent: The clinical relevance of these findings is unknown.

In vitro and in vivo genetic toxicology tests with ursodeoxycholic acid were negative.

The tests with ursodeoxycholic acid revealed no relevant evidence of a mutagenic effect.

d) Toxicity to reproduction

In studies in rats, tail malformations occurred after a dose of 2000 mg of ursodeoxycholic acid per kg of body weight. In rabbits, no teratogenic effects were found, although there were embryotoxic effects (from a dose of 100 mg per kg of body weight). Ursodeoxycholic acid had no effect on fertility in rats and did not affect peri-/post-natal development of the offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:

Povidone (Kollidon K-30) (E1201)

Sodium Lauril Sulphate (E487)

Maize Starch

Magnesium Stearate (E572)

Capsule Shell:

Gelatin (E441)

Titanium Dioxide (E 171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Colourless PVC film with aluminium blister foil packed in cardboard cartons.

Capsules are available in packs of 20, 28, 30, 50, 56, 60, 100 and 120 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Strides Acrolab International Limited

Unit 4, Metro Centre,

Tolpits Lane,

Watford,

Hertfordshire WD18 9SS,

United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA1650/014/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 31st January 2014

10 DATE OF REVISION OF THE TEXT

March 2016