For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

URSETOR SR

1. Generic Name

Ursodeoxycholic Acid Sustained Release Tablet 450 mg

2. Qualitative and quantitative Composition:

Each film coated sustained release tablet contains:

Ursodeoxycholic acid I.P……450 mg

Excipients……..…q.s.

Colour: Sunset Yellow FCF & Titanium dioxide I.P

The excipients used are Methocel LV, Methocel, Sodium Starch Glycolate, Microcrystalline Cellulose, Sodium Lauryl Sulphate, Lactose Monohydrate, Hydroxypropyl Methylcellulose, Purified talc, Magnesium Stearate, Colloidal Silicon Dioxide, Lake Sunset Yellow.

3. Dosage form and strength

Dosage form: film coated tablet

Strength: 450 mg

4. Clinical particulars

4.1. Therapeutic Indication

For the dissolution of radiolucent cholesterol gallstone, chronic cholestatic liver diseases in paricular primary biliary cirrhosis, primary sclerosing cholangitis and cholestasis associated with cyatic fibrosis.

4.2. Posology and method of administration

Dosage: As directed by the Physician.

There are no age restrictions on the use of Ursetor SR tablets in the treatment of PBC and for the dissolution of radiolucent gallstones.

The following daily dose is recommended for the various indications:

For the treatment of primary biliary cirrhosis (PBC)

The daily dose depends on body weight and ranges from 1½ to 3½ tablets (14 ± 2 mg of UDCA per kg of body weight).

For the first 3 months of treatment, Ursetor SR tablets should be taken divided over the day. With improvement of the liver values the daily dose may be taken once daily in the evening.

Body weight (kg)	Daily dose (mg/kg BW)	Film-coated tablets			
		first 3 months			subsequently
		morning	midday	evening	evening (1 x daily)
47 – 62	12 – 16	½	½	½	1½
63 – 78	13 – 16	½	½	1	2
79 – 93	13 – 16	½	1	1	2½
94 – 109	14 - 16	1	1	1	3
Over 110		1	1	1½	3½

The tablets should be swallowed with some liquid. The tablets should not be crushed or chewed. Care should be taken to ensure that they are taken regularly.

The use of Ursetor SR tablets in PBC may be continued indefinitely.

For dissolution of cholesterol gallstones:

Approximately 10mg of UDCA per kg of body weight, equivalent to:

up to 60 kg	1 tablet
61-80 kg	1½ tablets
81-100 kg	2 tablets
over 100 kg	2½ tablets

The tablets should be swallowed with some liquid in the evening at bedtime. The tablets should not be crushed or chewed. The tablets must be taken regularly.

The time required for dissolution of gallstones is generally 6-24 months, depending on stone size and composition. If there is no reduction in the size of the gallstones after 12 months, the therapy should not be continued.

The success of the treatment should be checked by means of ultrasound or X-ray examination every 6 months. At the follow-up examinations, a check should be made to see whether calcification of the stones has occurred in the meantime. Should this be the case, the treatment must be ended.

The likelihood of recurrence of gallstones after dissolution by bile acid treatment has been estimated as up to 50% at 5 years. The efficiency of Ursetor SR in treating radio-opaque or partially radio-opaque gallstones has not been tested but these are generally thought to be less soluble than radiolucent stones. Non-cholesterol stones account for 10-15% of radiolucent stones and may not be dissolved by bile acids.

Older people: In both indications 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

Both indications are very rare in children and adolescents. Therefore, there are no adequate data on the efficacy and safety in this population.

The administration of Ursetor SR is based on body weight and the medical condition.

For the treatment of hepatobiliary disorders associated with cystic fibrosis

Children with cystic fibrosis aged 6 to 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 tablets should not be used in patients with:

- Acute inflammation of the gall bladder or bile ducts.
- Occlusion of the biliary tract (occlusion of the common bile duct or a cystic duct).
- Frequent episodes of biliary colic.
- X-ray radiolucent calcified gallstones.
- Impaired contractility of the gallbladder.
- Hypersensitivity to bile acids or to any of the excipient listed in section 6.1.

- Active gastric and duodenal ulcers.

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 tablets should be taken under medical supervision.

During the first three months of the 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 cholangitis, this monitoring would also enable an early detection of potential hepatic deterioration, particularly in patients with advanced primary biliary cholangitis.

In order to be able to assess the therapeutic progression of the dissolution of gallstones and to timely identify a possible calcification of the stones, the gall bladder, depending on the size of the stones, should be visualized 6 to 10 months after the start of the treatment (oral cholecystography) with total image and occlusions and in the standing and lying position (ultrasound investigation).

If the gallbladder cannot be visualized on X-rays, or in cases of calcified gallstones, impaired contractility of the gall bladder or frequent episodes of biliary colic, the treatment with Ursodeoxycholic acid should be discontinued.

When used for the treatment of advanced primary biliary cholangitis:

In very rare cases decompensation of liver cirrhosis is observed which partially decreased after treatment discontinuation.

In patients with PBC, the clinical symptoms may worsen in rare cases at the start of treatment, e.g. pruritus may increase. In this case, the therapy is to be continued with a dose reduction and subsequently should be gradually increased to the recommended dose as described in Posology section.

If diarrhoea occurs, the dosage should be reduced, and treatment should be discontinued in case of persistent diarrhoea.

Female patients who use Ursodeoxycholic acid for dissolving gall stones must use an effective non-hormonal method of contraception, since hormonal contraception may increase biliary lithiasis.

4.5. Drugs interactions

Ursodeoxycholic acid tablets should not be used concurrently with colestyramine, colestipol, or an antacid, on the basis of aluminium hydroxide and/or smectite (aluminium oxide), because these preparations bind ursodeoxycholic acid in the intestine and thereby inhibits its absorption and efficacy. If the use of such a medicine is necessary, must it be taken at least 2 hours before or after <Product name>.

Ursodeoxycholic acid may affect the absorption of ciclosporin from the intestine. In patients treated with ciclosporin the blood level of ciclosporin should be monitored and the ciclosporin dose should be adjusted, if necessary.

In isolated cases Ursodeoxycholic acid can reduce the absorption of ciprofloxacin.

In a clinical study in healthy volunteers, the concomitant use of UDCA (500 mg/day) and rosuvastatin (20 mg/day) resulted in slightly elevated plasma levels of rosuvastatin.The clinical relevance of this interaction, also with other statins, is not known.

Ursodeoxycholic acid has been shown to reduce the peak plasma concentration (Cmax) and the AUC of the calcium antagonist nitrendipine in healthy volunteers. Close monitoring of the outcome of concurrent use of nitrendipine and ursodeoxycholic acid is recommended. An increase of the dose of nitrendipine may be necessary. An interaction with a reduction of the therapeutic effect of dapsone was also reported. .

These observations, together with in vitro findings could be an indication that ursodeoxycholic acid can induce cytochrome P450 3A enzymes. Induction has, however not been observed in a well-designed interaction study with budesonide, which is a known cytochrome P450 3A substrate.

Oestrogens and blood cholesterol lowering agents such as clofibrate increase hepatic cholesterol secretion and may therefore encourage biliary lithiasis; which is a counter-effect to ursodeoxycholic acid used for dissolution of gallstones.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy

There are no or limited amount of data from the use of ursodeoxycholic acid in pregnant women. Studies in animals have shown reproductive toxicity during the early gestation phase.

Ursodeoxycholic acid must not be used during pregnancy, unless clearly necessary.

Women of childbearing potential

Women of childbearing potential should be treated with ursodeoxycholic acid, only if they practice reliable contraception: non-hormonal contraceptives or oral contraceptives with low oestrogen dose are recommended. However, in patients taking Ursodeoxycholic acid for dissolving gallstones an 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.

Breastfeeding

According to few documented cases of breastfeeding women milk levels of ursodeoxycholic acid levels in milk are very low and probably no adverse reactions are to be expected in breastfed infants.

Fertility

Animal studies did not show an influence of ursodeoxycholic acid on fertility. Human data on fertility treatment with ursodeoxycholic acid are not available.

4.7. Effects on ability to drive and use machines.

Ursodeoxycholic acid has no or negligible influence on the ability to drive and use machines.

4.8. Undesirable effects

Most adverse effects are mild and tend to diminish with continued therapy.

The following adverse reactions have been reported during clinical trials and are ranked using the following frequency:

very common (≥1/10); common (≥1/100 to <1/10);

uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000);

not known (cannot be estimated from the available data).

Gastrointestinal disorders:

In clinical studies, reports of pasty stools or diarrhoea during treatment with ursodeoxycholic acid were common.

In very rare cases, severe right upper abdominal pain has occurred during the treatment of primary biliary cholangitis.

Hepatobiliary disorders:

During treatment with ursodeoxycholic acid calcification of gallstones can occur in very rare cases.

During the treatment of advanced stages of primary biliary cholangitis decompensation of cirrhosis has been observed in very rare cases, which partially regressed after treatment discontinuation.

Hypersensitivity reactions:

Very rarely urticaria may occur.

Reporting of 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. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

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

If diarrhoea occurs, the dosage should be reduced, and treatment should be discontinued in case of persistent diarrhoea.

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

Additional information or special populations

Long-term, high-dose UDCA therapy (28-30 mg/kg/day) by patients with primary sclerosing cholangitis (off-label use) was associated with a higher frequency of serious adverse events.

5. Pharmacological properties

5.1. Mechanism of Action

Ursodeoxycholic acid, a naturally occurring bile acid found in small quantities in normal human bile and in the bile of certain other mammals. It suppresses hepatic synthesis and secretion of cholesterol, and also inhibits intestinal absorption of cholesterol.

5.2. Pharmacodynamic properties

Pharmacotherapeutic group: Bile acid preparations

Bile acids are among the most important components of the bile and play a role in the stimulation of bile secretion. Bile acids are also important to keep the cholesterol in bile in solution. In a healthy person, the ratio between the concentration of cholesterol and bile acids in the bile is such that the cholesterol will remain in solution for most of the day. In this case, no gallstones can form (the bile is non-lithogenic). In patients with cholesterol stones in the bile, this ratio is changed and the bile is supersaturated with cholesterol (bile is lithogenic). This may cause a precipitation of cholesterol crystals and the formation of gallstones after some time.

The ursodeoxycholic acid converts lithogenic bile in non-lithogenic bile and gradually dissolves the cholesterol gallstones.

Investigations of the effect of ursodeoxycholic acid on the cholestasis in patients with impaired biliary drainage and on the clinical symptoms in patients with primary biliary cholangitis and cystic fibrosis have shown that cholestatic symptoms in the blood (to be measured by the increased value of alkaline phosphatase (AF), gamma- GT and bilirubin) and the itch declined rapidly, while also the fatigue decreased in the majority of patients. Moreover, studies seem to indicate a positive benefit-risk ratio of the ursodeoxycholic acid in children and young adult cystic fibrosis patients with mild to moderate hepatobiliary disorders.

Paediatric population

Cystic fibrosis

From clinical reports long-term experience of 10 years and more has been gained with UDCA therapy in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with UDCA can inhibit bile duct proliferation, can halt progression of histological damage and even reverse hepato-biliary changes, if it happens at an early stage of CFAHD. The treatment with UDCA should be started as soon as the CFAHD diagnosis is made, in order to optimize the effectiveness of the treatment.

5.3. Pharmacokinetic properties

About 90% of the therapeutic dose of the ursodeoxycholic acid is rapidly absorbed in the small intestine after oral administration.

After the absorption, ursodeoxycholic acid is absorbed in the liver (there is a substantial "first-pass-effect"), where it is conjugated with glycine or taurine and then secreted into the bile ducts. Only a small portion of ursodeoxycholic acid is found in the systemic circulation. This is excreted renally. With the exception of conjugation, ursodeoxycholic acid is not metabolised. However, a small fraction of orally administered ursodeoxycholic acid undergoes bacterial conversion to 7-keto- lithocholic acid resp. lithocholic acid after each enterohepatic circulation, while bacterial deconjugation also takes place in the duodenum. Ursodeoxycholic acid, 7- keto-lithocholic acid and lithocholic acid are relatively poorly soluble in water, so a large part of it is excreted via the bile into the faeces. Resorbed ursodeoxycholic acid is conjugated again by the liver; 80% of the lithocholic acid formed in the duodenum is excreted in the faeces, but the remaining 20% of it are sulphated by the liver to insoluble lithocholylconjugates after absorption, which in turn are excreted via the bile and faeces.

Resorbed 7-keto-lithocholic acid is reduced to chenodeoxycholic acid in the liver.

Lithocholic acid can cause cholestatic liver damage, when the liver is unable to sulphate the lithocholic acid. Although a reduced capacity to sulphate the lithocholic acid in the liver is found in some patients, there is for the time being no clinical evidence that cholestatic liver damage can be associated with the therapy using ursodeoxycholic acid.

After repeated dosage, the ursodeoxycholic acid concentration in the bile reaches a "steady state" after approximately 3 weeks: the total concentration of the ursodeoxycholic acid, however, is never higher than about 60% of the total concentration of the bile acid in the bile: also at high doses.

After therapy with ursodeoxycholic acid is stopped, the concentration of ursodeoxycholic acid in bile decreases quickly after 1 week to 5-10% of the "steady- state" concentration.

The biological half-life of ursodeoxycholic acid is approximately 3.5 to 5.8 days.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

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

Long-term studies in mice and rats revealed no evidence of ursodeoxycholic acid having carcinogenic potential. 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

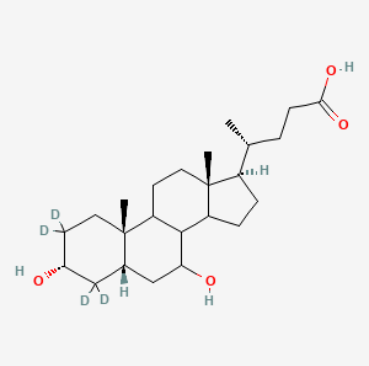
In studies in rats, tail malformations occurred after a dose of 2000 mg per kg of body weight.

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.

7. Description

Ursodeoxycholic acid

Ursodeoxycholic acid is (4R)-4-[(3R,5S,7S,10S,13R,17R)-2,2,4,4-tetradeuterio-3,7-dihydroxy-10,13-dimethyl-3,5,6,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl]pentanoic acid. The empiric formula of $C_{24}H_{40}O_4$ and its molecular weight is 396.6 g/mol. Its structural formula is:



Ursetor SR 450

Ursodeoxycholic Acid Sustained Release tablets are Orange coloured, Capsuled shaped, biconvex, film coated sustained release tablet having scored on one side.

The excipients used are Methocel LV, Methocel, Sodium Starch Glycolate, Microcrystalline Cellulose, Sodium Lauryl Sulphate, Lactose Monohydrate, Hydroxypropyl Methylcellulose, Purified talc, Magnesium Stearate, Colloidal Silicon Dioxide, Lake Sunset Yellow

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

URSETOR 450 is available in pack of 10 tablets.

8.4. Storage and handing instructions

Store protected from light and moisture at a temperature not exceeding 30ºC.

Keep out of reach of children

Swallow whole table. Do not crush, Chew or break.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies.
- Have kidney or liver problems.
- Are pregnant or plan to become pregnant.
- Are breastfeeding or plan to breastfeed.
- Have any serious illness.
- Are taking any medicines (prescription, over the counter, vitamins, or herbal products)

10. Details of manufacturer

Ravenbhel Biotech

EPIP, SIDCO, Kartholi, Bari Brahmana, Jammu – 181 133

11. Details of permission or licence number with date

Mfg. Licence No: JK/01/11-12/192 Issued on: 29.07.2015

12. Date of revision

Feb 2026

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/URSETOR SR 450/Feb-2026/03/PI