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

URSETOR SR

(**Ursodeoxycholic Acid Sustained Release Tablet 450mg)**

COMPOSITION

URSETOR 450

Each film-coated (S.R.) tablet contains:
Ursodeoxycholic Acid.…450mg

INDICATIONS

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.

POSOLOGY AND METHOD OF ADMINISTRATION

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
Paediatric population
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

CONTRAINDICATIONS
Ursetor SR tablets 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 cystic duct)
- Frequent episodes of biliary colic
- Radio-opaque calcified gallstones
- Impaired contractility of the gall bladder
- Hypersensitivity to bile acids or any excipient of the formulation

When used in hepatobiliary disorders associated with cystic fibrosis in children aged 6 to 18 years:
- Unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Ursetor SR tablets 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 PBC, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advanced stage PBC.

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.

In patients with PBC, in rare cases the clinical symptoms may worsen at the beginning of treatment, e.g. the itching may increase. In this case the dose should be reduced to 250mg daily and then gradually increased to the recommended dose. If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued.

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, Ursetor SR should not be used.

Female patients taking Ursetor SR for dissolution of gallstones should use an effective non-hormonal method of contraception, since hormonal contraceptives may increase biliary lithiasis

DRUG-INTERACTION

Ursetor SR should not be administered concomitantly with colestyramine, colestipol or antacids containing aluminium hydroxide and/or smectite (aluminium oxide), because these preparations bind UDCA 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 Ursetor SR.

Ursetor SR can affect 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, Ursetor SR can reduce the absorption of ciprofloxacin.

UDCA has been shown to reduce peak plasma concentrations (C_{max}) and area under the curve (AUC) of the calcium antagonist nitrendipine in healthy volunteers. Close monitoring of the outcome of concurrent use of nitrendipine and UDCA 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 indicate a potential for UDCA to 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.

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

FERTILITY, PREGNANCY AND LACTATION
Animal studies did not show an influence of UDCA on fertility. Human data on fertility effects following treatment with UDCA are not available.

Pregnancy
There are no or limited amounts of data from the use of UDCA in pregnant women. Studies in animals have shown reproductive toxicity during the early phase of gestation Ursetor SR must not be used during pregnancy unless clearly necessary.

Women of childbearing potential
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 Ursetor SR 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.

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
UDCA has no or negligible influence on the ability to drive and use machines.

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

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: */ Not known (:< 1/10,000 / cannot be estimated from available data)*	

Hepatobiliary disorders:
During treatment with UDCA, calcification of gallstones can occur in very rare cases.
During therapy of the advanced stages of PBC, in very rare cases decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.

Gastrointestinal disorders:
In clinical trials, reports of pasty stools or diarrhoea during UDCA therapy were common.
Very rarely, severe right upper abdominal pain has occurred during the treatment of PBC

Skin and subcutaneous tissue disorders:
Very rarely, urticaria can occur.

OVERDOSE
Diarrhoea may occur in cases of overdose. In general, other symptoms of overdose are unlikely because the absorption of UDCA 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.

Additional information on special populations:
Long-term, high-dose UDCA therapy (28-30 mg/kg/day) in patients with primary sclerosing cholangitis (off-label use) was associated with higher rates of serious adverse events.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties
Pharmacotherapeutic group/ATC code
Group: Bile acid preparations
Code: A05AA02
Small amounts of UDCA are found in human bile.
After oral administration, it reduces cholesterol saturation of the bile by inhibiting cholesterol absorption in the intestine and decreasing cholesterol secretion into the bile. Presumably as a result of dispersion of the cholesterol and formation of liquid crystals, a gradual dissolution of cholesterol gallstones occurs.

According to current knowledge, the effect of UDCA in hepatic and cholestatic diseases is thought to be due to a relative exchange of lipophilic, detergent-like, toxic bile acids for the hydrophilic, cytoprotective, non-toxic UDCA, to an improvement in the secretory capacity of the hepatocytes, and to immune-regulatory processes.

Cystic fibrosis - Paediatric population
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 optimise treatment effectiveness.

Pharmacokinetic properties
UDCA 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.

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 UDCA, 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 UDCA having carcinogenic potential.

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

The tests with UDCA 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). UDCA had no effect on fertility in rats and did not affect peri-/post-natal development of the offspring.

EXPIRY DATE

Do not use later than the date of expiry.

STORAGE

Store at a temperature not exceeding 30^{o}C, Protected from moisture. Keep out of reach of children.

PRESENTATION

Available in strip pack of 10 tablets.

MARKETED BY:

torrent PHARMA

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