

PRESCRIBING INFORMATION

1. TRADE NAME OF THE MEDICINAL PRODUCT

Ursolit 100 mg tablets

Ursolit 300 mg tablets

2. COMPOSITION

Each Ursolit 100 mg tablet contains: Ursodeoxycholic acid 100 mg

Each Ursolit 300 mg tablet contains: Ursodeoxycholic acid 300 mg

Ursolit 100mg also contains 75 mg Lactose monohydrate.

Ursolit 300mg also contains 100 mg Lactose monohydrate.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets for oral administration.

Appearance:

Ursolit 100: white round biconvex scored tablets.

Ursolit 300: white round biconvex scored tablets.

4. CLINICAL PARTICULARS.

4.1 Therapeutic Indications

Dissolution or reduction in size of radiolucent cholesterol in patient with a functioning gallbladder.

Treatment of chronic liver diseases including primary billiary cirrhosis, primary sclerosing cholangitis, cystic fibrosis associated liver disease, billiary atresia, chronic hepatitis, and alcohol cirrhosis.

4.2 Posology and method of administration

Gallstone dissolution: 8 to 12 mg/kg/day given in 2 divided doses.

If doses are unequal the larger dose should be taken in late evening to counteract the rise in biliary cholesterol saturation which occurs in the early morning. The late evening dose may usefully be taken with food to help maintain bile flow overnight.

The time required for dissolution of gallstones is likely to range from 6 to 24 months depending on stone size and composition. Follow-up cholecystograms or ultrasound investigation may be useful at 6 month intervals until the gallstones have disappeared. Treatment should be continued until 2 successive cholecystograms and/or ultrasound investigations 4-12 weeks apart have failed to demonstrate gallstones. This is because these techniques do not permit reliable visualisation of stones less than 2mm in diameter.

The efficiency of Ursolit 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% radiolucent stones and may not be dissolved by bile acids.

Chronic liver diseases: 10 to 15 mg/kg/day administered in 2 to 4 divided doses with food.

The dose may be adjusted according to the patient's age and severity of symptoms.

4.3 Contra-indications:

Ursolit tablets should not be used in patients:

- With hypersensitivity to bile acids or any of the excipients listed in section 6.1
- With radio-opaque calcified gallstones
- With occlusion of the biliary tract (occlusion of the common bile duct or cystic duct).
- With acute inflammation of the gall bladder or biliary tract.
- With frequent episodes of biliary colic
- With impaired contractility of the gall bladder.
- With chronic liver disease, peptic ulcers or in those with inflammatory diseases of the small intestine and colon.

4.4 Special warnings and precautions for use:

- Ursolit should be taken under medical supervision.
- During the first 3 months of treatment, the 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 the 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, Ursolit 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 diarrhea occurs, the dose must be reduced and in cases of persistent diarrhea, the therapy should be discontinued.
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactose deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction:

- Ursodeoxycholic acid should not be administered concomitantly with charcoal, 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.
- Ursodeoxycholic acid 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 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 inductive effect on cytochrome P450 3A enzymes.
- Oral contraceptives, 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 Pregnancy and lactation

Animal studies did not show an influence of UDCA on fertility (see section 5.3). 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 (see section 5.3). URSOLIT 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 URSOLIT tablets 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.

4.7 Effects on ability to drive and use machines

No effects on ability to drive and use machines have been observed.

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:

In clinical trials, reports of pasty stools or diarrhea during ursodeoxycholic acid therapy were common.

Very rarely, severe right upper abdominal pain has occurred during the treatment of primary biliary cirrhosis.

Ursodeoxycholic acid may give rise to nausea and vomiting. The frequency of these effects are not known.

Hepatobiliary disorders:

During treatment with ursodeoxycholic acid, calcification of gallstones can occur in very rare cases making them unable to be dissolved by bile acid therapy and resulting in surgery for some patients.

During therapy of the advanced stages of primary biliary cirrhosis, in very rare cases decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.

Skin and subcutaneous disorders:

Very rarely, urticaria can occur.

Ursodeoxycholic acid may give rise to pruritus. The frequency of this effect is not known.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (<http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il>).

4.9 Overdose:

Diarrhea 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

Pharmacotherapeutic group: Bile acid preparation

ATC code: A05AA02

5.1 Pharmacodynamics properties:

Ursolit is naturally occurring bile acid found in small quantities in normal human bile and in larger quantities in the biles of certain species of bears. Ursolit suppresses hepatic synthesis and cholesterol secretion and also inhibits intestinal absorption of cholesterol. It has little inhibitory effect on synthesis and secretion into bile of endogenous bile acids and does not appear to affect phospholipid secretion into bile.

Although insoluble in aqueous media, cholesterol may be solubilized in at least 2 ways in the presence of dihydroxy bile acids. In addition to solubilizing cholesterol in micelles, Ursolit acts by an apparently unique mechanism to cause dispersion of cholesterol as liquid crystals in aqueous media. Thus even though administration of high doses (eg, 15 to 18 mg/kg/day) does not result in concentration of ursodeoxycholic acid higher than 60% of the total bile acid pool, ursodeoxycholic acid rich bile solubilizes cholesterol. The overall effect of Ursolit is to increase the concentration level at which saturation of cholesterol occurs. The various actions of Ursolit combine to change the bile of patients with gallstones from cholesterol – precipitating to cholesterol – solubilizing.

5.2 Pharmacokinetic properties:

Absorption/Distribution - Ursodeoxycholic acid is absorbed in the small bowel after oral administration. After absorption ursodeoxycholic acid enters the portal vein and undergoes extraction from portal blood by the liver (ie, "first – pass" effect) where it is conjugated with glycine or taurine and is then secreted into the hepatic bile ducts. In the bile it is concentrated in the gallbladder and expelled into the duodenum in gallbladder via the cystic and common ducts by gallbladder contractions provoked by physiologic responses to eating. With repeated

dosing, bile ursodeoxycholic acid concentrations reach steady state in about 3 weeks. After ursodeoxycholic acid dosing is stopped, its concentration in bile falls exponentially, declining to about 5% to 10% of its steady-state level in about 1 week.

Metabolism/Excretion – Small quantities of ursodeoxycholic acid appear in the systemic circulation, and very small amounts are excreted into urine. A small portion of orally administered drug undergoes bacterial degradation with each cycle of enterohepatic circulation. Ursodeoxycholic acid can be oxidized and reduced, yielding 7-keto-lithocholic acid or lithocholic acid respectively. Free ursodeoxycholic acid, 7-keto-lithocholic acid, and lithocholic acid are relatively insoluble in aqueous media, and larger proportions of these compounds are excreted via the feces. Reabsorbed free ursodeoxycholic acid is reconstituted by the liver. Eighty percent of lithocholic acid formed in the small bowel is excreted in the feces, but the 20% that is adsorbed is sulfated in the liver to relatively insoluble lithocholyl conjugates that are excreted into the bile and lost in feces. Absorbed 7-keto-lithocholic acid is stereospecifically reduced in the liver to chenodiol.

6. PHARMACEUTICAL PARTICULARS

6.1 Ursolit 100 excipients: Lactose monohydrate, Carboxymethyl-Cellulose Calcium, Maize Starch, Povidone, Magnesium Stearate

Ursolit 300 excipients: Lactose monohydrate, Maize Starch, Povidone, Magnesium Stearate, Colloidal Silicone Dioxide

6.2 Special precautions for storage: Do not store above 25 °C.

7. MANUFACTURER/ MARKETING AUTHORIZATION HOLDER:

CTS Chemical Industries Ltd., 3 Hakidma St., Kiryat Malachi

8. MARKETING AUTHORIZATION NUMBER:

Ursolit 100: 0192520542

Ursolit 300: 0586326923

9. DATE OF REVISION OF THE TEXT:09.2017