URSOBLITZ™

Ursodeoxycholic acid Tablets IP 300mg

1. Generic Name

Ursodeoxycholic acid 300mg

2. Qualitative and Quantitative composition:

Each uncoated tablet contains:

Ursodeoxycholic acid IP 300mg

(In Betacyclodextrin base)

Excipients..... q.s

3. Dosage form and strength:

Dosage: Ursoblitz Tablets is available in oral dosage form.

Strength: Each uncoated tablet of Ursoblitz contains Ursodeoxycholic acid 300mg (In Betacyclodextrin base)

4. Clinical particulars

4.1. Therapeutic indication

For the dissolution of Radiolucent cholesterol gall stone, chronic cholestatic liver disease in particular primary biliary cirrhosis, primary sclerosing cholangitis & cholestasis associated with cystic fibrosis.

4.2. Posology and method of administration

Dosage

The dosage should be calculated based on the patient's body weight. The calculated dosage should be rounded to the nearest number of tablets.

- **Dissolving of cholesterol stones**

Usual dosage: 8 to 10 mg/kg/day, corresponding to, for example, four to six 150 mg tablets, or two to three tablets of 300 mg, or two tablets of 450 mg. The daily dose can be administered two or three times after the meals: two tablets should always be taken after the evening meal.

Also, a single evening dose can be selected (e.g., a patient of 60 kg, in the evening two tablets of 300 mg). Preferably, this single dose should be taken one hour before bedtime and ± two hours after the evening meal with a glass of milk or a small snack.

The duration of the treatment to obtain lysis of the gallstones depends on their size but is usually not shorter than three to four months. To assess the result of the therapy properly, it is necessary to determine the size of the stones accurately at the start of the treatment and to check this further regularly, for example every six months, by means of a new contrast X-ray recording and/or sonographic recording.

In patients in whom, after six months of treatment with the indicated dosage, the stones are not reduced in size, it is recommended to determine the lithogenic index in the bile by means of a duodenum drainage. When 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 the gallstones.

Treatment should be continued for three to four months after it is established by means of ultrasound check that the gallstones are completely dissolved. An interruption of the treatment for three to four weeks results in a return to over-saturation of the bile and prolongs the overall duration of the therapy. The interruption of the treatment after the dissolving of the gallstones can be followed by a recurrence.

- **Primary Biliary Cholangitis**

The dosage of ursodeoxycholic acid in primary biliary cholangitis (stages I-III), amounts to 12-15 mg/kg/day, which is equivalent to four to eight tablets of 150 mg, two to four tablets of 300 mg, to be taken in two to three portions during the day, or with two tablets of 450 mg, to be taken in two portions during the day.

The dosage of ursodeoxycholic acid in primary biliary cholangitis stage IV and an increase of the serum bilirubin contents (> 40 µg/l), should be in the first instance, only a half of the normal dose (6 to 8 mg/kg/day). Thereafter, the liver function should be closely monitored for several weeks (once every two weeks for six weeks). If there is no deterioration of the liver function [AF (or ALP) Alkaline Phosphatase, Alanine Aminotransferase (ALT) (SGPT), Aspartate Aminotransferase(AST)(SGOT), Gamma-Glutamyl Transferase (γ-GT), bilirubin] and no increase in itching occurs, the dose may be further increased to the usual level. Moreover, the liver function must then again be closely monitored for several weeks. If again no deterioration of the liver function takes place, the patient may be held at the normal dosage for a long time.

In patients with primary biliary cholangitis stage IV without elevated serum bilirubin, the usual starting dose is allowed to be administered directly. Anyway, here too an accurate control of the liver function should be executed.

The treatment of the primary biliary cholangitis should be regularly assessed based on liver values (laboratory) and clinical findings.

Method of administration: Oral

If the patient has difficulty in swallowing because of the size of the tablet, the tablet can be halved, if necessary, on the dividing score, so that one half tablet can be taken twice directly in sequence.

4.3. Contraindication

Ursodeoxycholic Acid

Ursodeoxycholic acid should not be used in patients with:

- Hypersensitivity or intolerance to active substance or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
- 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
- X-ray radiolucent calcified gallstones
- Active gastric and duodenal ulcers
- Impaired contractility of the gall bladder
- Widespread intrahepatic obstruction

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.

- **When used for dissolving gallstones:**

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 section 4.2.

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 (see sections 4.5 and 4.6).

Carcinogenesis and Mutagenesis

Ursodeoxycholic acid has no carcinogenic, mutagenic or teratogenic effects in laboratory animals treated at higher doses than those intended for therapy in humans, and after long-term treatment.

Hepatic/Biliary/Pancreatic

Patients with variceal bleeding, hepatic encephalopathy, ascites, or in need of an urgent liver transplant, should receive appropriate specific treatment. Caution should be exercised when Ursodeoxycholic acid is administered in a setting of partial biliary obstruction of extra-hepatic origin.

4.5. Drug interactions

Ursodeoxycholic acid tablets should not be used concurrently with cholestyramine, colestipol, or an antacid, based on 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 Ursodeoxycholic acid.

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.

Administration of ursodeoxycholic acid for 14 days also significantly increased total bilirubin by 139 ± 39% (p=0.003), conjugated bilirubin by 127 ± 29% (p=0.005) and unconjugated bilirubin by 151 ± 52% (p=0.004). The proposed biological mechanism for this interaction is that bilirubin and rosuvastatin are both metabolites of organic anion transporting polypeptide 1B1 (OATP1B1). OATP1B1 expression is regulated by transcription factor hepatic nuclear factor (HNF) 1α. ursodeoxycholic acid acts as an inhibitor of HNF 1α and consequently may decreased expression of OAT1B1. A dose reduction in rosuvastatin should be considered in any individuals exposed to both rosuvastatin and ursodeoxycholic acid. The clinical relevance of this interaction about other statins is unknown. However, it is biologically possible that this interaction may also occur between ursodeoxycholic acid and other statins which are known substrates of OAT1B1, such as atorvastatin, fluvastatin, simvastatin acid, pitavastatin and pravastatin.

4.6 Use in special population

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 directed by physician.

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.

Use in renal impairment.

The effect of ursodeoxycholic acid in patients with renal impairment has not been studied.

Paediatric

The safety and effectiveness of ursodeoxycholic acid in children has not been established.

Geriatrics

Appropriate studies with ursodiol have not been performed in the geriatric population. However, geriatric-specific problems that would limit the use or usefulness of ursodiol in the elderly are not expected.

4.7. Effects on ability to drive and use machine.

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

4.8. Undesirable effects:

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.

Some patients may experience increased pruritus in the early weeks of treatment. In such cases a dose reduction, and thereafter a slow (weekly) increase of dose to the recommended dose, may help.

Other adverse reactions reported include increased cholestasis, nausea, vomiting and sleep disturbance.

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.

Serious adverse effects are also unlikely to occur in overdosage. However, liver function should be monitored. If necessary, ion-exchange resins may be used to bind bile acids in the intestines.

Additional information or special populations

Long-term, high-dose ursodeoxycholic acid 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 (Ursodiol), a naturally occurring hydrophilic bile acid, derived from cholesterol, is present as a minor fraction of the total human bile acid pool. Oral administration of ursodiol increases this fraction in a dose related manner, to become the major biliary acid, replacing/displacing toxic concentrations of endogenous hydrophobic bile acids that tend to accumulate in cholestatic liver disease.

Multiple mechanisms of action at the cellular and molecular level in addition to the replacement and displacement of toxic bile acids include cytoprotection of the injured bile duct epithelial cells (cholangiocytes) against toxic effects of bile acids, inhibition of apoptosis of hepatocytes, immunomodulatory effects via a number of mechanisms including decreasing expression of MHC class I proteins on hepatocytes and cholangiocytes, and stimulation of bile secretion by hepatocytes and cholangiocytes.

The cholesterol-lowering effect observed following the administration of ursodiol in patients with primary biliary cirrhosis could be related to an improvement of cholestasis, modifications in cholesterol metabolism, or both. Changes in the endogenous bile acid composition induced by ursodiol might be the common denominator of these two mechanisms.

5.2. Pharmacodynamic properties

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 ursodeoxycholic acid therapy in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with ursodeoxycholic acid 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 ursodeoxycholic acid should be started as soon as the CFAHD diagnosis is made, 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. Except for 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 lithocholyl conjugates 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.

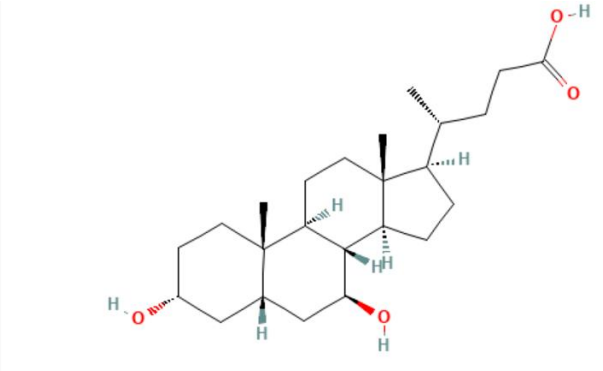
6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology: Not Applicable

7. Description

Ursodeoxycholic acid is a bile acid found in the bile of bears (Ursidae) as a conjugate with taurine. Used therapeutically, it prevents the synthesis and absorption of cholesterol and can lead to the dissolution of gallstones. It has a role as a human metabolite and a mouse metabolite. It is a conjugate acid of an ursodeoxycholate. The IUPAC chemical name of ursodeoxycholic acid is 3α, 7β-dihydroxy-5β-cholan-24-oic acid. The empirical formula is $C_{24}H_{40}O_4$ and its molecular weight is approximately 392.6 g/mol.

The chemical structure of ursodeoxycholic acid is as follows:



8. Pharmaceutical particulars

8.1 Incompatibilities

There are no known incompatibilities.

8.2 Shelf-life: 24 Months

8.3 Packaging Information

10 tablets per strip of Ursoblitz.

8.4 Storage and handling instructions

Store below 25 ^{0}C, protect from light & moisture. Keep out of reach of children.

9. Patient Counselling Information

9.1 Adverse reactions: Refer part 4.8.

9.2 Drug Interactions: Refer part 4.5.

9.3 Dosage: Refer part 4.2.

9.4 Storage: Refer part 8.4.

9.5 Risk factors: Refer part 4.4.

9.6 Self-monitoring information: NA

9.7 Information on when to contact a health care provider or seek emergency help.

Patient is advised to be alert for the emergence or worsening of the adverse reactions and contact the prescribing physician.

9.8 Contraindications: Refer part 4.3.

10. Details of manufacturer:

AEON FORMULATIONS PVT.LTD.,
R.S. No.515/1, 515/2 & 514, No. 152/7,
Vinayagar Koil Street, Thirubuvanaipalayam,
Mannadipet Commune, Puducherry – 605 107, India.

11. Details of permission or license number with date:

Mfg.Lic.No.: 12/13/3242

Date: 31/10/2022

12. Date of revision: September 2025