URSODEOXYCHOLIC ACID

URSOLIV

℞

500 mg Film-Coated Tablet

Bile and Liver Therapy (Bile acids and derivative)

FORMULATION:
Each film-coated tablet contains:
Ursodeoxycholic acid 500 mg

PHARMACODYNAMIC PROPERTIES:
The mechanism of Ursodeoxycholic acid's anticholelithic action is not completely understood, it is known that when administered orally Ursodeoxycholic acid is concentrated in bile and decreases biliary cholesterol saturation by inhibiting its intestinal absorption. The reduced cholesterol saturation permits the gradual solubilization of cholesterol from gallstones resulting in their eventual dissolution. Ursodeoxycholic acid increases bile flow. In chronic cholestatic liver disease, Ursodeoxycholic acid appears to reduce the detergent properties of the bile salts thus reducing their cytotoxicity. Also, Ursodeoxycholic acid may protect liver cells from the damaging activity of toxic bile acids (e.g. lithocholate. deoxycholate. and chenodeoxycholate) which increase in concentration in patients with chronic liver disease.

PHARMACOKINETIC PROPERTIES :
Ursodeoxycholic acid is absorbed from the small bowel (about 90% of dose).
Ursodeoxycholic acid is extensively bound to plasma proteins.
Hepatic (first-pass hepatic clearance). Exogenous Ursodeoxycholic acid is metabolized in the liver to its taurine and glycine conjugates. The resulting conjugates are secreted into bile.
Time to peak concentration is 1 to 3 hours.
The half life of administered Ursodeoxycholic acid is 3.5-5.8 days.
The excretion of Ursodeoxycholic acid is primarily fecal; very small amounts are excreted into urine. Small amount of unabsorbed Ursodeoxycholic acid passes into the colon where it undergoes bacterial degradation (7-dehydroxylation); resulting lithocholic acid is partly absorbed from the colon but is sulfated in the liver and rapidly eliminated in the feces as the sulfolithocholyl glycine or sulfolithocholyl taurine conjugate.

Indications:
For the dissolution of cholesterol-rich gallstones in the bladder and for the treatment of biliary reflux gastritis and cholestatic liver disease.
For the symptomatic treatment of primary biliary cirrhosis (PBC), in patients without decompensated hepatic cirrhosis.

Dosage and mode of administration
There are no age restrictions on the use of Ursodeoxycholic acid (Ursoliv) tablets in the treatment of PBC and for the dissolution of radiolucent gallstones.

The following daily dose is recommended for the various indications:
<u>For dissolution of cholesterol gallstones</u>
Approx. 10 mg of ursodeoxycholic acid per kg of body weight, equivalent to:

up to 60 kg	1 film-coated tablet
61-80 kg	1 ½ film-coated tablets
81-100 kg	2 film-coated tablets
over 100 kg	2 ½film-coated tablets

The film-coated tablets should be swallowed whole with some liquid the evening at bedtime. They must be taken regularly.

The film-coated tablets should be swallowed whole with some liquid in the evening at bedtime. They must be taken regularly. The time required for the dissolution of gallstones is generally 6-24 months. 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.

<u>For the symptomatic treatment of Primary Biliary Cirrhosis (PBC)</u>
The daily dose depends on body weight and ranges from 1 ½ to 3 ½ film-coated tablets (14 ± 2 mg of ursodeoxycholic acid per kg of body weight).
For the first 3 months of treatment Ursodeoxycholic Acid (Ursoliv) film-coated tablets should be taken divided over the day. When the liver function parameters improve, the daily dose may be taken once daily in the evening.

Body weight (kg)	Ursodeoxycholic Acid (Ursoliv) film-coated tablets			
	first 3 months			subsequently
	morning	midday	evening	evening (1x daily)
47 - 62	½	½	½	1 ½
63 - 78	½	½	1	2
79 - 93	½	1	1	2 ½
94 - 109	1	1	1	3
Over 110	1	1	1 ½	3 ½

The film-coated tablets should be swallowed whole with me liquid. They must be taken regularly.
The use of Ursodeoxycholic Acid (Ursoliv) film coated tablets in primary biliary cirrhosis may be continued indefinitely.
In patients with primary biliary cirrhosis, in rare cases the clinical symptoms may worsen at the beginning of treatment, e.g. the itching may increase. In this event, therapy should first be continued with half an Ursodeoxycholic Acid (Ursoliv) film coated tablets daily, and the dose then gradually increased (weekly increase of the daily dose by half a film-coated tablet until the dose indicated in the respective dosage regimen is reached again .

Contraindications:
Ursodeoxycholic Acid (Ursoliv) film coated 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

Interactions:
Ursodeoxycholic Acid (Ursoliv) film coated tablets 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 (Ursoliv) film coated tablets .
Ursodeoxycholic Acid (Ursoliv) film coated tablets can affect the absorption of ciclosporin from the intestine. In patients receiving ciclosporin treatment, blood concentrations

of this substance should therefore be checked by physician and the ciclosporin dose adjusted if necessary.
In isolated cases, Ursodeoxycholic Acid (Ursoliv) film coated tablets can reduce the absorption of ciprofloxacin.
In a clinical study in healthy volunteers 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 regard to other statins is unknown.
UDCA has been shown to reduce peak plasma concentrations (Cmax) 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, Pregnancy and Lactation. 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. Ursodeoxycholic acid (Ursoliv) 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 Ursodeoxycholic acid (Ursoliv) for dissolution of gallstones, effective non-hormonal contraception should be used, sincehormonal 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 inbreastfed infants.

Special warnings and precautions for use:
Ursodeoxycholic Acid (Ursoliv) film-coated tablets should be taken under medical supervision.
During the first 3 months of treatment, liver function parameters AST (SGOT). ALT (SGPT) and -g-GT should be monitored by the physician every 4 weeks, thereafter every 3 months. Apart from allowing for identification of responders or 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 (Ursoliv) film-coated tablets should not be used.
When used for treatment of the advanced stages of primary biliary cirrhosis:
In very rare cases decompensation of the hepatic cirrhosis has been observed; which partially regressed after the treatment discontinued. If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued.
Female patients taking UDCA 500mg film-coated tablets for dissolution of gallstones should use an effective non-hormonal method of contraception, since hormonal contraceptives may increase biliary lithiasis.
In patients with PBC, in rare cases the clinical symptoms may worsen at the beginning of treatment, e.g. the itching may increase.
Long-term, high-dose UDCA therapy (28-30 mg/kg/day) in patients with primary sclerosing cholangitis was associated with higher rates of serious adverse events.

Side Effects:
The evaluation of undesirable effects is based on the followingfrequency 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 (< 1/10,000), not known (cannot be estimated from the available data)

Gastrointestinal disorders:
In clinical trials, reports of pasty stools or diarrhoea during ursodeoxycholic acid therapy were common. Very rarely, severe; right upper abdominal pain has occurred during the treatment of primary biliary cirrhosis.
Hepatobiliary disorders: During treatment with ursodeoxycholic acid, calcification of gallstones can occur in very rare cases.
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 tissue disorders: Very rarely, urticaria can occur.

Overdosage and Treatment:
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.

Storage: Store at temperatures not exceeding 30ºC in a dry place, away from direct sunlight.

Packaging: PVC-PVDC/Alu Blister Pack x 10's (Box of 50's)

Note:
Read the instructions carefully before use.
Do not use the product after the expiry date.
Do not use the product if there are any significant changes in appearance of the tablets.
Keep out of reach of children.

Caution : Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:
MEGA LIFESCIENCES Public Company Limited
515/1 Moo 4, Soi 8, Bangpoo Industrial Estate,
Pattana 3 Road, Phraeksa, Mueang,
Samutprakarn 10280, Thailand

Manufactured under license from:
MEGA LIFESCIENCES (AUSTRALIA) PTY. LTD.
60, National Avenue, Pakenham,
Victoria 3810, Australia

Imported by:
MEGA LIFESCIENCES LIMITED INC.
Unit 5B 5/F BA Lepanto Bldg., 8747 Paseo de Roxas,
Bel-Air, Makati City, Philippines

Distributed by: **METRO DRUG. INC**
Sta. Rosa Estate, Barangay Macabling,
Santa Rosa, Laguna, Philippines

DR-XY49075

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Date of First Authorization: 17 MAY 2024
Date of Revision of Package Insert: MAY 2024

I-U502-M25-00-00