

## **1. Name of the medicinal product**

Ursoliv 500

## **2. Qualitative and Quantitative composition**

Each film-coated tablet contains 500 mg Ursodeoxycholic acid

## **3. Pharmaceutical form**

White colored oblong shape film coated tablets

## **4. Clinical particulars**

### **4.1 Therapeutic indications**

For the treatment of primary biliary cirrhosis (PBC), provided there is no decompensated hepatic cirrhosis.

For the dissolution of cholesterol gallstones in the gall bladder. The gallstones must not show as shadows on X-ray images and should not exceed 15 mm in diameter. The gall bladder must be functioning despite the gallstone(s).

Paediatric population

Hepatobiliary disorders associated with cystic fibrosis in children aged 6 to 18 years

### **4.2 Posology and method of administration**

There are no age restrictions on the use of Ursoliv 500 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 1.5 to 3.5 tablets (14 ± 2 mg of UDCA per kg of body weight).

For the first 3 months of treatment, Ursoliv 500 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 UDCA (mg/kg. BW) | Ursoliv 500 mg Film coated tablets |        |         |                   |
|------------------|-----------------------------|------------------------------------|--------|---------|-------------------|
|                  |                             | First 3 months                     |        |         | Subsequently      |
|                  |                             | Morning                            | Midday | Evening | Evening (1xdaily) |
| 47-62            | 12-16                       | 0.5                                | 0.5    | 0.5     | 1.5               |
| 63-78            | 13-16                       | 0.5                                | 0.5    | 1       | 2                 |
| 79-93            | 13-16                       | 0.5                                | 1      | 1       | 2.5               |
| 94-109           | 14-16                       | 1                                  | 1      | 1       | 3                 |
| Over 110         |                             | 1                                  | 1      | 1.5     | 3.5               |

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 Ursoliv 500 in PBC may be continued indefinitely.

**For dissolution of cholesterol gallstones:**

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

|             |             |
|-------------|-------------|
| up to 60 kg | 1 tablet    |
| 61-80 kg    | 1.5 tablets |
| 81-100 kg   | 2 tablets   |
| over 100 kg | 2.5 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 Ursoliv 500 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 Ursoliv 500 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

| Body weight (kg) | Daily dose UDCA (mg/kg. BW) | Ursoliv 500 mg Film coated tablets |        |         |
|------------------|-----------------------------|------------------------------------|--------|---------|
|                  |                             | Morning                            | Midday | Evening |
| 20 – 29          | 17-25                       | 0.5                                | -      | 0.5     |
| 30 – 39          | 19-25                       | 0.5                                | 0.5    | 0.5     |
| 40 – 49          | 20-25                       | 0.5                                | 0.5    | 1       |
| 50 – 59          | 21-25                       | 0.5                                | 1      | 1       |
| 60 – 69          | 22-25                       | 1                                  | 1      | 1       |
| 70 – 79          | 22-25                       | 1                                  | 1      | 1.5     |
| 80 – 89          | 22-25                       | 1                                  | 1.5    | 1.5     |
| 90 – 99          | 23-25                       | 1.5                                | 1.5    | 1.5     |
| 100 – 109        | 23-25                       | 1.5                                | 1.5    | 2       |
| > 110            |                             | 1.5                                | 2      | 2       |

### 4.3 Contraindications

Ursoliv 500 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

### 4.4 Special warnings and precautions for use

Ursoliv 500 should be taken under medical supervision:

During the first 3 months of treatment, liver function parameters AST (SGOT), ALT (SGPT) and  $\gamma$ -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 described in section 4.2.

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, Ursoliv 500 should not be used.

Female patients taking Ursoliv 500 for dissolution of gallstones should use an effective non-hormonal method of contraception, since hormonal contraceptives may increase biliary lithiasis (see section 4.5. and 4.6.)

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

Ursoliv 500 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 Ursoliv 500

Ursoliv 500 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, Ursoliv 500 can reduce the absorption of ciprofloxacin.

In a clinical study in healthy volunteers concomitant use of UDCA (500mg/day) and rosuvastatin (20mg/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 (C<sub>max</sub>) 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.

#### **4.6 Fertility, 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). Ursoliv 500 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-estrogen oral contraceptive measures are recommended. However, in patients taking Ursoliv 500 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

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

### 4.8 Undesirable effects

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

|  |   |
|--|---|
| <b>Very common:</b> ( $\geq 1/10$ )  | <b>Common:</b> ( $\geq 1/100$ to $< 1/10$ )   |
| <b>Uncommon:</b> ( $\geq 1/1000$ to $< 1/100$ )  | <b>Rare:</b> ( $\geq 1/10000$ to $< 1/1000$ ) |
| <b>Very rare:</b> / Not known ( $< 1/10000$ / 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.

#### Reporting of suspected 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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system



#### **4.9 Overdose:**

Diarrhea 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 diarrhea 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.

### **5. Pharmacological properties**

#### **5.1 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 – pediatric 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 optimize treatment effectiveness.

## **5.2 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.

## **5.3 Preclinical safety data**

### **a.) Acute toxicity**

Acute toxicity studies in animals have not revealed any toxic damage.

### **b.) Chronic toxicity**

Sub chronic 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

### **6. PHARMACEUTICAL PARTICULARS**

#### **6.1 List of excipients**

##### **Tablet core:**

Microcrystalline Cellulose 101

Povidone K30

Polysorbate 80

Crospovidone

Colloidal silicon dioxide

Talcum powder

Magnesium stearate

Purified water

##### **Film coating:**

Opadry II Complete Clear 52U19258

Talcum powder

Purified water

#### **6.2 Incompatibilities**

Not applicable

#### **6.3 Shelf life**

Please find the expiry date on the outer carton.

#### **6.4 Special precautions for storage**

Store below 30 °C in the original package in order to protect from light.

#### **6.5 Nature and contents of container**

10 tablets in aluminium-PVC/PVDC blister, 5 blisters in printed box with leaflet.

#### **7. Manufacturer**

Mega Lifesciences Public Company Limited

Samutprakarn, Thailand

#### **8. Marketing Authorization Number**

Reg. No. ....

#### **9. Date of revision of the text**

December 2020