# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT
Ursolit 100 mg tablets
Ursolit 300 mg tablets

## 2. QUALITATIVE AND QUANTITATIVE 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
- Radio-opaque calcified gallstones
- Occlusion of the biliary tract (occlusion of the common bile duct or cystic duct).
- Acute inflammation of the gall bladder or biliary tract.
- Frequent episodes of biliary colic
- Impaired contractility of the gall bladder.
- Active gastric and duodenal ulcers;

**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 cholangitis, this monitoring would also enable an early detection of potential hepatic deterioration, particularly in patients with advanced stage primary biliary cholangitis.

<u>When used for the dissolution of cholesterol gallstones:</u>

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, depending on stone size, the gall bladder should be visualised 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 gall bladder cannot be visualised on X-rays, or in cases of calcified gallstones, impaired contractility of the gall bladder or frequent episodes of biliary colic, the treatment with Ursolit should be discontinued.

<u>When used for treatment of advanced stage of primary biliary cirrhosis:</u>

In very rare cases decompensation of hepatic cirrhosis is observed, which partially decreased after the treatment was discontinued.

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 diarrhea occurs, the dose should be reduced and in cases of persistent diarrhea, the therapy should be discontinued.

When used for treatment of patients with primary sclerosing cholangitis:
Long-term, high-dose (more than recommended) ursodeoxycholic acid therapy (28-30 mg/kg/day) in patients with primary sclerosing cholangitis was associated with higher rates of serious adverse events.

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)

Excipient(s)
*Lactose*
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 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.

In a clinical study in healthy volunteers concomitant use of ursodeoxycholic acid (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.

Ursodeoxycholic acid has been shown to reduce the plasma peak concentrations (Cmax) and the area under the curve (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 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.

Oestrogens and blood cholesterol lowering agents such as clofibrate increase hepaticmcholesterol secretion and may therefore encourage biliary lithiasis, which is a counter-effect to ursodeoxycholic acid used for dissolution of gallstones.

**4.6 Fertility, pregnancy and lactation**

*Pregnancy*

There are no or limited amounts of data from the use of ursodeoxycholic acid 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 ursodeoxycholic acid 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 (see section 5.3). Human data on fertility effects following treatment with ursodeoxycholic acid are not available.

**4.7 Effects on ability to drive and use machines**

Ursodeoxycholic acid 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:

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)

**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.

Nausea, vomiting - Not known

**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 disorders:**

Very rarely, urticaria can occur.
Pruritus - 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 https://sideeffects.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.
If diarrhoea occurs, the dosage should be reduced, and treatment should be discontinued in case of persistent diarrhoea.
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**
**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: Bile acid preparations, ATC code: A05AA02

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.

<u>Paediatric population</u>
<u>Cystic fibrosis</u>
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, in order to optimize the effectiveness of the treatment.

**5.2 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. With the exception of conjugation, ursodeoxycholic acid is not metabolised. However, a small fraction of orally administered ursodeoxycholic acid undergoes bacterial conversion to 7-ketolithocholic 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 lithocholylconjugates 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 "steadystate" concentration.

The biological half-life of ursodeoxycholic acid is approximately 3.5 to 5.8 days.

**5.3 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 ursodeoxycholic acid, 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 ursodeoxycholic acid having carcinogenic potential. In vitro and in vivo genetic toxicology tests with

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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1

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

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

### 6.2 Special precautions for storage:

Do not store above 25 $^{0}$ C.

### 6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

## 7. MANUFACTURER/ MARKETING AUTHORIZATION HOLDER:

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

## 8. MARKETING AUTHORIZATION NUMBER:

Ursolit 100: 019-25-20542

Ursolit 300: 058-63-26923

**9. DATE OF REVISION OF THE TEXT:** 11 2025