SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

URSOLISIN 150 mg hard capsules
URSOLISIN 300 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

150 mg hard capsules
Each capsule contains
Active substance
Ursodeoxycholic acid 150 mg

300 mg hard capsules
Each capsule contains
Active substance
Ursodeoxycholic acid 300 mg

For excipients, see paragraph 6.1

3. PHARMACEUTICAL FORM

Hard capsules

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Qualitative or quantitative alterations to the cholepoietic function, including the forms with bile supersaturated with cholesterol, to contrast the formation of cholesterol calculi or to create suitable conditions for dissolution if radio-transparent calculi are already present; in particular cholecystic calculi in functioning cholecysts and calculi in bile duct deposited or recurring following operations on the biliary tracts; biliary dyspepsia.

4.2. Posology and method of administration

The availability of 150 and 300 mg packaging permits different dosage regimes, useful in the various clinical conditions for which this preparation is recommended. In prolonged use to reduce the lithogene characteristics of bile, the average daily dosage is 5-10 mg/Kg: in most cases, the daily dosage is between 300 and 600 mg, equal to 2-4 150 mg capsules per day, with also the possibility of using 1 capsule of 300 mg twice a day (morning and evening); to maintain suitable conditions for dissolving already present calculi, the treatment must last for at least 4-6 months and may even last 12 months or more. For dyspeptic syndromes and maintenance therapy, doses of 150 mg, once or twice a day are generally sufficient.
Doses can be modified depending on the Doctor's opinion; in particular, the excellent tolerability of the preparation permits the administration of considerably higher doses.
Administration should preferably take place during or after meals.

4.3. Contraindications

Ursolisin should not be used in patients with:

- **a.** Acute inflammation of the gall bladder or bile ducts
- **b.** obstruction of the biliary tract (common or cystic bile duct obstruction)
- **c.** frequent episodes of biliary colic
- **d.** radio-opaque calcified stones
- **e.** impaired motility of the gallbladder
- **f.** hypersensitivity to bile acids or to any of the excipients.

4.4. Special warnings and precautions for use

Ursolisin must be used under medical supervision.

During the first 3 months of treatment, liver function tests AST (SGOT), ALT (SGPT) and γ-GT must be monitored by a doctor every 4 weeks and thereafter every 3 months. In addition to enabling the identification of responders and non-responders to treatment of primary biliary cirrhosis, such monitoring should also favour early diagnosis of potential liver damage, particularly in patients with advanced-stage primary biliary cirrhosis.

When used to for the dissolution of cholesterol stones:
In order to prove the therapeutic improvement and the timely identification of any calcification of the stones, depending on their size, the gallbladder must be visualized (oral cholecystogram) with an overview and the occluded ducts in the orthostatic and supine position (ultrasound control) 6-10 months after the initiation of treatment.

If the gallbladder cannot be seen with X-ray images, or in the case of calcified stones, contractility of the damaged gallbladder, or frequent episodes of biliary colic, Ursolisin should not be used.

The female patients that take Ursolisin for the dissolution of the calculations must use an effective non-hormonal contraception as hormonal contraceptives may increase biliary lithiasis (see paragraph 4.5 and 4.6).

When used for the treatment of advanced stage primary biliary cirrhosis:
In very rare cases a liver cirrhosis decompensation has been observed, which partially regressed after cessation of treatment.

In patients with PBC (primary biliary cirrhosis), in rare cases, the clinical symptoms may worsen at the start of treatment, for example itching can increase. In this case the ursodeoxycholic acid dose should be reduced to a 250 mg capsule per day and subsequently increased gradually as described in section 4.2

In the case of diarrhea, the dose should be reduced and in case of persistent diarrhea, treatment must be discontinued.

4.5. Interactions with other medicinal products and other forms of interaction
Ursolisin should not be co-administered with cholestyramine, colestipol or antacids containing aluminium hydroxide and/or smectite (aluminium oxide) since they bind the ursodeoxycholic acid in the intestine and thus inhibit its absorption and effectiveness. If the use of a compound containing any of these substances is necessary, it must be taken at least 2 hours before or after taking Ursolisin.

Ursolisin may increase the intestinal absorption of cyclosporine. Therefore the blood concentration of patients being treated with cyclosporine should be monitored by the doctor and the cyclosporine dosage should be adjusted, if necessary.

In isolated cases Ursolisin may reduce the absorption of ciprofloxacin.

In a clinical study on healthy volunteers, concomitant use of ursodeoxycholic acid (500 mg/day) and rosuvastatin (20 mg/day) resulted in slightly higher plasma levels of rosuvastatin. The clinical relevance of this interaction, also as regards the other statins, is not known.

Ursodeoxycholic acid has been shown to reduce the peak plasma concentration (C_{max}) and area under the curve (AUC) of the calcium antagonist nitrendipine on healthy volunteers. It is recommended a careful monitoring of the outcome due to the use of concomitant nitrendipine and ursodeoxycholic acid. It may be necessary to increase the dose of nitrendipine. In addition, an interaction with a reduction of the therapeutic effect of dapsone was also reported. These observations, together with in vitro tests indicate a potential induction of the 3A enzymes of the cytochrome P450 by ursodeoxycholic acid. Controlled clinical trials have shown, however, that ursodeoxycholic acid does not have a significant inductive effect on the 3A enzymes of the cytochrome P450.

Estrogenic hormones and serum cholesterol reducing agents such as clofibrate may increase gallstone formation, and hence may counteract the effectiveness of ursodeoxycholic acid used to dissolve stones.

4.6. Fertility, pregnancy and lactation
Animal studies have not shown any influence of ursodeoxycholic acid on fertility (see section 5.3). Human data are not available on the effects on fertility following treatment with ursodeoxycholic acid.
They do not exist or are limited data on the use of ursodeoxycholic acid in pregnant women.
Studies in animals have shown a teratogenic effect during the initial stage of gestation. (see section 5.3).
Ursolisin should not be used during pregnancy unless absolutely necessary.
Women of childbearing age should be treated only if they use a reliable form of contraception: non-hormonal or low estrogens oral contraceptives are recommended. However, in patients taking Ursolisin for the dissolution of stones, an effective non-hormonal method of contraception should be used, since oral hormonal contraceptives may increase gallstone formation. Before starting treatment pregnancy must be ruled out.

According to the few documented cases of women who breastfeed, levels of ursodeoxycholic acid in breast milk are very low and are probably not to be expected adverse reactions in breast-fed babies.

4.7. Effects on the ability to drive and use machines

Ursodeoxycholic acid has no or ha negligible influence on the ability to drive or use machinery.

4.8. Adverse reactions

The evaluation of side effects is based on the following frequencies:
Very common (≥ 1/10),
Common (≥ 1/100, < 1/10),
Uncommon (≥ 1/1000, < 1/100),
Rare (≥ 1/10000, < 1/1000),
Very rare / Not known (<1/10000 / the frequency cannot be estimated from available data).

Gastrointestinal disorders:
In clinical trials, reports of soft faeces or diarrhea during treatment with ursodeoxycholic acid have been common.
Very rarely, during treatment of primary biliary cirrhosis, severe abdominal pain occurred in the upper right quadrant.

Hepatobiliary disorders:
In very rare cases, calcification of gallstones may occur during treatment with ursodeoxycholic acid. In very rare cases during the treatment of advanced stage primary biliary cirrhosis, a liver cirrhosis decompensation has been observed, which partially regressed after cessation of treatment.

Skin and subcutaneous tissue disorders:
Very rarely, hives can occur.

4.9. Overdose

In the case of overdose, diarrhea may occur. In general, other symptoms of overdose are unlikely because the absorption of ursodeoxycholic acid decreases with an increased dose and is then mostly excreted in the faeces.

Specific countermeasures are not required and the consequences of diarrhea should be treated symptomatically with fluid and electrolyte reintegration.

Additional information on special populations:
The long-term treatment with ursodeoxycholic acid at high doses (28-30 mg/kg/day) in patients with primary sclerosing cholangitis (unauthorized use of said *off-label*) has been associated with a higher frequency of serious adverse events.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic Group: Hepatobiliary antilytogenic, litolytic, ATC code A05AA02
The active substance of the drug is ursodeoxycholic acid, a biliary acid physiologically present as colic acid or kenodeoxycholic acid in human bile. Ursodeoxycholic acid in use clinically for some time in the treatment of various biliary tract affections has recently been recognised as being able to increase the solubilising capacity of bile against cholesterol by transforming lithogene bile into non-lithogene bile. The clinical therapeutic activity of the drug concerns the ability to de-saturate lithogene bile and to correct the alterations of the cholepoitic function with the effect of contrasting the formation of calculi and of creating suitable conditions for their dissolution, if already present; these properties also permit the drug to act on dyspeptic symptoms which accompany these forms, rapidly and highly effectively. The absence of undesired effects suggests that ursodeoxycholic acid may be safer and better accepted than previous calculus lytic treatments.

5.2. Pharmacokinetic properties

Following oral administration, ursodeoxycholic acid is absorbed by the gastro-intestinal tract both with a passive mechanism on a dejunum and colon level and with an active mechanism at the ileus level. The hepatic clearance is high: the drug is mainly metabolised on a hepatic level. It is excreted in the bile, in conjugate form, in the entero-hepatic circle and partly with the faeces.

5.3. Preclinical safety data

The acute toxicity tests in rats and mice demonstrated that the product, taken orally, has very low toxicity (LD50 in mice > 6000 mg/Kg). The prolonged toxicity tests for 24 weeks in rats and dogs demonstrated the good tolerability of

ursodeoxycholic acid. No foetal toxicity or damaging effects on gastric mucous or intestinal motility were found in the experimented animal, even at doses in excess of the therapeutic dose.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Maize starch; Sodium starch glycolate; Silica colloidal anhydrous; Magnesium stearate.
Capsule composition: pure gelatine, Titanium dioxide.

6.2. Incompatibilities

They are neither reported in literature nor found in clinical practice. (Refer to paragraph 4.5)

6.3. Shelf life

3 years.

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and content of container

Self-blocking hard gelatine capsules in aluminium and PVC blisters.
150 mg hard capsules - 20 capsules
150 mg hard capsules - 30 capsules
150 mg hard capsules - 40 capsules
300 mg hard capsules - 10 capsules
300 mg hard capsules - 20 capsules
300 mg hard capsules – 100 capsules

Not all packages are marketed.

6.6. Instructions fo use

The unused product and/or any waste material should be disposed of in accordance with local requirements in force.

7. MARKETING AUTHORISATION HOLDER

Aesculapius Farmaceutici S.r.l. - Via Cefalonia, 70 - 25124 Brescia.

8. MARKETING AUTHORISATION NUMBERS

150 mg hard capsules - 20 capsules M.A. n° 025430063
150 mg hard capsules - 30 capsules M.A. n° 025430075
150 mg hard capsules - 40 capsules M.A. n° 025430087
300 mg hard capsules - 10 capsules M.A. n° 025430099
300 mg hard capsules - 20 capsules M.A. n° 025430101
300 mg hard capsules - 100 capsules M.A. n° 025430113

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Renewal date: June 2010

10. DATE OF REVISION OF THE TEXT

May 2023