1. Name of the medicinal product
Ursocol Tablets 150mg / 300
Ursodeoxycholic Acid Tablets 150mg / 300mg

2. Qualitative and quantitative composition
Ursodeoxycholic acid (URSODEOXYCHOLIC ACID TABLETS) Ph. Eur. 150mg / 300mg per tablet.

3. Pharmaceutical form
Tablets.

4. Clinical particulars
4.1 Therapeutic indications
Ursodeoxycholic Acid Tablets 150mg / 300mg are indicated for the dissolution of radiolucent cholesterol-rich gallstones in adults, including the elderly, and children with a functioning gallbladder.
Ursodeoxycholic Acid Tablets 150mg / 300mg are indicated for hepatobiliary disorder associated with cystic fibrosis in children aged 6 years to less than 18 years.
4.2 Posology and method of administration
Posology
Dissolution of radiolucent cholesterol-rich gallstones:
A daily dose of 8-10mg/kg (3 or 4 tablets of Ursodeoxycholic Acid Tablets 150mg per day for most patients) is recommended. Obese patients may require a higher dose of Ursodeoxycholic Acid Tablets (up to 15mg/kg/day).
This should be taken in two divided doses after meals, with at least half the dose being taken after the evening meal.
The time required for dissolution of gallstones is generally in the range of 6-24 months, and is dependent on the size and composition of the stones. Treatment should be regularly monitored (by cholecystograms) and continued for 3-4 months following the disappearance of the gallstones. Stones may recur after successful treatment. The time required to effect stone dissolution may be increased if Ursodeoxycholic Acid Tablets is temporarily discontinued (for 3-4 weeks) during treatment.
The dose of Ursodeoxycholic Acid Tablets for elderly patients and for children should be related to body weight (8-10mg/kg/day).
Children with cystic fibrosis aged 6 years to less than 18 years:
20mg/kg/day in 2-3 divided doses, with a further increase to 30mg/kg/day if necessary.
Method of administration
For oral use.
4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
URSODEOXYCHOLIC ACID 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 a cystic duct)
- frequent episodes of biliary colic
- impaired contractility of the gall bladder.

URSODEOXYCHOLIC ACID TABLETS is not suitable for the dissolution of radio-opaque calcified gallstones.
URSODEOXYCHOLIC ACID TABLETS should not be used in patients who are pregnant, or may become pregnant.
URSODEOXYCHOLIC ACID TABLETS should not be used in patients with active gastric or duodenal ulcers, or with intestinal or hepatic disorders which interfere with the enterohepatic circulation of bile acids e.g. ileal resection and stoma, regional ileitis, extra and intrahepatic cholestasis, severe, acute and chronic liver diseases.
Paediatric population
Unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia.

4.4 Special warnings and precautions for use

URSODEOXYCHOLIC ACID TABLETS should be taken under medical supervision.
During the first three months of treatment, the liver function parameters AST (SGOT), ALT (SGPT) and γ-GT should be monitored by the physician every four weeks, thereafter every three months.
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) six to ten 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 TABLETS should not be used.
Female patients taking URSODEOXYCHOLIC ACID TABLETS for dissolution of gallstones should use an effective non-hormonal method of contraception, since hormonal contraceptives may increase biliary lithiasis (see sections 4.5. and 4.6.).
If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued.
Excessive dietary intake of calories and cholesterol should be avoided.
This product contains lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

URSODEOXYCHOLIC ACID TABLETS should not be administered concomitantly with colestyramine, colestipol, charcoal or antacids containing aluminium hydroxide and/or smectite (aluminium oxide), because these preparations bind URSODEOXYCHOLIC ACID TABLETS 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 two hours before or after URSODEOXYCHOLIC ACID TABLETS.
URSODEOXYCHOLIC ACID 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 the physician and the ciclosporin dose adjusted if necessary.
In isolated cases URSODEOXYCHOLIC ACID TABLETS can reduce the absorption of ciprofloxacin.
In a clinical study in healthy volunteers concomitant use of URSODEOXYCHOLIC ACID TABLETS (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.
There is a potential for URSODEOXYCHOLIC ACID TABLETS to induce cytochrome P450 3A enzymes as indicated by a report of an interaction with a reduction of the therapeutic effect of dapsone, as well as *in vitro* findings. Induction has, however, not been observed in a well-designed interaction study with budesonide, which is a known cytochrome P450 3A substrate.
Estrogenic hormones, estrogen rich oral contraceptives 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 TABLETS used for dissolution of gallstones.

4.6 Fertility, pregnancy and lactation

Fertility
Animal studies did not show an influence of URSODEOXYCHOLIC ACID TABLETS on fertility. Human data on fertility effects following treatment with URSODEOXYCHOLIC ACID TABLETS are not available.
Pregnancy
There are no or limited amounts of data from the use of URSODEOXYCHOLIC ACID TABLETS in pregnant women. Studies in animals have shown reproductive toxicity during gestation (see section 5.3). URSODEOXYCHOLIC ACID TABLETS is contraindicated

in pregnancy (see section 4.3). Women of childbearing potential should be treated only if they are using reliable contraception; non-hormonal or low-oestrogen oral contraceptive measures are recommended. However, in patients taking URSODEOXYCHOLIC ACID 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 TABLETS 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

URSODEOXYCHOLIC ACID TABLETS 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	
Common	Reports of pasty stools or diarrhoea in clinical trials
Hepatobiliary disorders	
Very rare	Calcification of gallstones
Skin and subcutaneous tissue disorders	
Very rare	Urticaria

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 Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Diarrhoea may occur in cases of overdose. In general, other symptoms of overdose are unlikely because the absorption of URSODEOXYCHOLIC ACID TABLETS 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. However, ion-exchange resins may be used to bind bile acids in the intestines. It is recommended that liver function tests are monitored.

Additional information on special populations:

Long-term, high-dose URSODEOXYCHOLIC ACID TABLETS 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: bile acids and derivatives, ATC code: A05AA02.

URSODEOXYCHOLIC ACID TABLETS is a bile acid, normally only present as a very small proportion (up to 5%) of the total biliary bile acids. Oral administration of URSODEOXYCHOLIC ACID TABLETS increases this fraction in a dose-related manner and URSODEOXYCHOLIC ACID TABLETS may become the major biliary bile acid (40-50%). URSODEOXYCHOLIC ACID TABLETS decreases biliary lipid cholesterol secretion, mainly due to a reduction in the absorption of cholesterol from the intestine. There appear to be

no effects on cholesterol or bile acid biosynthesis. Cholesterol is gradually solubilised from the gallstones.

Paediatric population

Cystic fibrosis

From clinical reports long-term experience up to 10 years and more is available with URSODEOXYCHOLIC ACID TABLETS treatment in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with URSODEOXYCHOLIC ACID TABLETS can decrease bile duct proliferation, halt progression of histological damage and even reverse hepato-biliary changes if given at early stage of CFAHD. Treatment with URSODEOXYCHOLIC ACID TABLETS should be started as soon as the diagnosis of CFAHD is made in order to optimise treatment effectiveness.

5.2 Pharmacokinetic properties

URSODEOXYCHOLIC ACID TABLETS is detected in plasma within 10-40 minutes of oral administration. URSODEOXYCHOLIC ACID TABLETS is only moderately soluble in the upper small intestine but is well absorbed in the jejunum and ileum. Peak levels are seen at approximately 1 and 3 hours. URSODEOXYCHOLIC ACID TABLETS shows hepatic first pass clearance of approximately 60% (conjugation is predominantly with glycine). URSODEOXYCHOLIC ACID TABLETS is rapidly excreted into bile. Glycine-conjugated URSODEOXYCHOLIC ACID TABLETS may be hydrolysed to free URSODEOXYCHOLIC ACID TABLETS. That which is not absorbed undergoes bacterial conversion to lithocholic acid, the main bacterial degradation product which is poorly absorbed into bile. Another metabolite, 7-ketolithocholic acid may be reabsorbed and transformed in the liver to URSODEOXYCHOLIC ACID TABLETS and lithocholic acid. URSODEOXYCHOLIC ACID TABLETS and its metabolites are excreted in the faeces.

5.3 Preclinical safety data

A similar drug to URSODEOXYCHOLIC ACID TABLETS has been found to be carcinogenic in animals. The relevance of these findings to the clinical use of URSODEOXYCHOLIC ACID TABLETS has not been established. Embryotoxicity associated with the use of URSODEOXYCHOLIC ACID TABLETS has been observed in rabbits so URSODEOXYCHOLIC ACID TABLETS is contra-indicated in pregnancy.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose BP/Ph. Eur
Crospovidone (XL, Type A) BP/Ph. Eur
Povidone (k-30) BP/Ph. Eur
Purified Water BP/Ph. Eur
Magnesium stearate BP/Ph. Eur

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Strip pack 3 * 10’s = 24 months

6.4 Special precautions for storage

Store up to 30°C, protected from light.

6.5 Nature and contents of container

White circular biconvex uncoated tablet with plain surface on one side and breakline on the other side contained within aluminium foil coated with LDPE;cold form buster laminate and al foil with polyester/paper laminate.
Pack sizes: 30 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Sun Pharmaceutical Industries Limited
Sun House, Plot No. 201 B/1,
Western Express Highway,
Goregoan (E), Mumbai, Maharashtra,
India

8. Date of Preparation of text

23 June 2018.