SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ursogrix 250 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 250 mg ursodeoxycholic acid.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Capsule, hard.

White hard gelatin capsules size 0, approximately 21.7 mm x 7.64 mm. The content – white or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Dissolution of cholesterol gallstones in patients:
  - having one or more radiolucent (radio-negative) gallstones, preferably with a diameter of no more than 2 cm, in a properly functioning gallbladder;
  - refusing surgical intervention or for whom surgical procedures are not indicated;
  - in whom cholesterol supersaturation has been demonstrated by chemical testing on bile obtained via duodenal drainage.
  - As adjuvant medicine before and after gallstone shockwave dissolution (lithotripsy).
- Primary biliary cholangitis (PBC, also known as primary biliary cirrhosis).

Paediatric population
Hepatobiliary disorders as a result of cystic fibrosis in children and adolescents aged 6 to 18 years.

4.2 Posology and method of administration

Posology

Dissolution of gallstones (alone or in combination with lithotripsy).

The recommended daily dose is 8-10 mg/kg body weight of ursodeoxycholic acid, equivalent to 2-4 capsules, to be taken with a meal as follows:
- at a daily dose of 2 capsules: both capsules with an evening meal;
- at a daily dose of 3 capsules: 1 in the morning and 2 in the evening;
- at a daily dose of 4 capsules: 2 in the morning and 2 in the evening;

OR

take a daily dose of 2-4 capsules in the evening before bedtime.

The duration of the dissolution process with this medicinal product is 6 months to 2 years, depending on the initial size of the stones. For a proper assessment of the therapeutic outcome, it is necessary, at the start of treatment, to accurately determine the size of the existing stones and subsequently to monitor them regularly, for example, every 3-4 months, via new X-rays and/or ultrasound scans.

In patients whose stones have not decreased in size after 6 months of treatment at the dosage stated, it is recommended that the biliary lithogenic index be determined via duodenal drainage. If the bile has an index of >1.0, it is unlikely that a favourable outcome can be obtained and it is better to consider a different form of treatment for gallstones. Treatment must be continued for 3 to 4 months after ultrasound follow-up has confirmed complete dissolution of the gallstones.

Discontinuation of treatment

Discontinuation of treatment for 3-4 weeks leads to a return of bile supersaturation and prolongs the overall duration of therapy. Discontinuation of treatment after dissolution of the gallstones may be followed by a relapse.

Treatment of primary biliary cholangitis (PBC).

Stage I-III

The daily dose depends on body weight and ranges from 12-16 mg/kg body weight of ursodeoxycholic acid (3-7 capsules).
During the first 3 months of treatment this medicinal product should be taken in divided doses throughout the day. If liver function improves, the total daily dose can be taken once daily in the evening.

Body weight (kg)	Daily dose (mg/kg body weight)	Capsules			
		First 3 months			**Subsequently**
		Morning	Afternoon	Evening	Evening (once daily)
47-62	12-16	1	1	1	3
63-78	13-16	1	1	2	4
79-93	13-16	1	2	2	5
94-109	14-16	2	2	2	6
More than 110		2	2	3	7

Stage IV

In combination with increased serum bilirubin levels (> 40 µg/L; conjugated), only half the normal dosage (see dosage for stages I-III) should initially be given (6-8 mg/kg/day of ursodeoxycholic acid, equivalent to about 2-3 capsules).

Thereafter, liver function should be properly monitored for several weeks (once every 2 weeks for 6 weeks). If there is no deterioration in liver function (AP, ALAT, ASAT, gamma-GT, bilirubin) and if no increase in pruritus occurs, the dosage can be increased further to the usual level. However, liver function should again be closely monitored for several weeks. Once again, if there is no deterioration in liver function, the patient can be maintained at the normal dosage over the long term.

Patients with primary biliary cholangitis (stage IV) without increased serum bilirubin levels are permitted to receive the normal starting dose immediately (see dosage stages I-III).

However, close monitoring of liver function, as described above, is likewise applicable in such cases; treatment of PBC will need to be regularly assessed on the basis of liver parameters (laboratory) and clinical findings.
The use of this medicinal product in PBC is not limited in term of time.

Paediatric population

Children and adolescents with cystic fibrosis aged 6 to 18 years:
20 mg/kg/day of ursodeoxycholic acid in 2 to 3 divided doses, with an increase up to 30 mg/kg/day if necessary.

Body weight (kg)	**Daily dose (mg/kg body weight)**	**Ursogrix 250 mg hard capsules**		
		Morning	**Afternoon**	**Evening**
20-29	17-25	1	--	1
30-39	19-25	1	1	1
40-49	20-25	1	1	2
50-59	21-25	1	2	2
60-69	22-25	2	2	2
70-79	22-25	2	2	3
80-89	22-25	2	3	3
90-99	23-25	3	3	3
100-109	23-25	3	3	4
>110		3	4	4

Method of administration

For oral use.

The capsules should be swallowed whole with some liquid. The medicine should be used regularly.
For patients weighing less than 47 kg or patients who are unable to swallow Ursogrix, other formulations with ursodeoxycholic acid are available.

4.3 Contraindications

- Hypersensitivity to the active substance, bile acids or to any of the excipients listed in section 6.1;
- acute inflammation of the gallbladder or biliary tract;
- biliary tract occlusion (occlusion of the common bile duct or a cystic duct);
- repeated biliary colic;
- radio-opaque calcified gallstones;
- impaired contractility of the gallbladder.

Paediatric population:
- unsuccessful portoenterostomy or missing recovery of normal bile flow in children with biliary atresia.

4.4 Special warnings and precautions for use

Ursodeoxycholic acid should be used under medical supervision.

During the first 3 months of treatment, liver function parameters AST (SGOT), ALT (SGPT), ALP and γ-GT should be monitored by the physician every 4 weeks, and every 3 months thereafter. As well as allowing for differentiation between responsive and non-responsive patients treated for PBC, this monitoring also enables early detection of potential deterioration in liver function, especially in patients with advanced PBC.

When used for dissolution of gallstones
In order to assess the therapeutic progression of gallstone dissolution and to promptly detect any calcification of the gallstones, the gallbladder should be visualised (oral cholecystography) 6-10 months after the start of treatment, depending on stone size, with overview and occlusions in standing and supine positions (ultrasound control).

If the gallbladder cannot be visualised on X-ray images, or in cases of calcified gallstones, impaired contractility of the gallbladder or frequent episodes of biliary colic, treatment with this medicinal product must be discontinued.

Female patients taking this medicinal product to dissolve gallstones should use an effective non-hormonal contraceptive, as hormonal contraceptives may promote the formation of gallstones (see sections 4.5 and 4.6).

When used to treat patients with advanced PBC
In very rare cases decompensation of liver cirrhosis has been observed, which partially regressed upon discontinuation of treatment.

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 dosage of this medicinal product can be reduced to one 250 mg capsule per day and subsequently should be gradually increased to the recommended dose as described in section 4.2.

If diarrhoea occurs, the dosage must be reduced and, in the event of persistent diarrhoea, treatment must be discontinued.

4.5 Interaction with other medicinal products and other forms of interaction

This medicine should not be used concomitantly with colestyramine, colestipol or antacids containing aluminium hydroxide and/or smectite (aluminium oxide), as these substances can bind Ursogrix in the intestine, thereby reducing absorption and efficacy. If the use of any such medicine is needed, it must be taken at least 2 hours before or after Ursogrix.

This medicinal product can affect the absorption of ciclosporin from the intestine. In patients treated with ciclosporin, blood levels of the latter must therefore be monitored by the physician and the ciclosporin dosage adjusted if necessary.
Due to the effect of ursodeoxycholic acid on the secretion of bile acids there is a theoretical possibility that the absorption of other lipophilic substances could be affected.

In isolated cases, Ursogrix can reduce the absorption of ciprofloxacin.

In a clinical study with healthy volunteers, concomitant use of this medicinal product (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.

This medicinal product reduces the peak plasma concentration (C_{max}) and the area under the curve (AUC) of the calcium antagonist nitrendipine in healthy volunteers. Close monitoring of the outcome of concomitant use of nitrendipine and Ursogrix is recommended. It may be necessary to increase the dosage of nitrendipine. An interaction with dapsone has also been reported, with a reduction in its therapeutic effect. These observations, together with *in vitro* data, might indicate that Ursogrix can induce cytochrome P450 3A enzymes. However, induction has not been observed in a well-designed interaction study with budesonide, a known cytochrome P450 3A substrate.

Oestrogens and blood cholesterol-lowering agents, such as clofibrate, increase hepatic cholesterol secretion and may thereby stimulate formation of gallstones; this effect is counteractive in the use of this medicinal product for gallstone dissolution.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited of data from the use of Ursogrix in pregnant women. Studies in animals have shown reproductive toxicity during the early phase of gestation (see section 5.3). Therefore, this medicinal product should not be used during pregnancy unless clearly necessary.

Women of childbearing potential
Women of childbearing potential may only be treated with Ursogrix if they use reliable contraception: non-hormonal contraception or oral contraception with a low oestrogen dosage is recommended. However, in patients using this medicinal product to dissolve gallstones, effective non-hormonal contraception should be used, as hormonal oral contraceptives can increase formation of gallstones (see section 4.4).
The possibility of a pregnancy must be excluded before beginning of the treatment.

Breast-feeding
According to a few documented cases of breastfeeding women, the amount of Ursogrix in milk was very low and no adverse reactions are to be expected in breastfed infants.

Fertility
Animal studies did not indicate any effect of this medicinal product on fertility (see section 5.3). Human data on fertility effects after treatment with this medicinal product are not available.

4.7 Effects on ability to drive and use machines

Ursogrix 250 mg hard capsules 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 frequencies: 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 available data).

Gastrointestinal disorders
Common: pasty stools or diarrhoea.
Very rare: severe right upper abdominal pain has occurred during treatment of PBC.

Hepatobiliary disorders
Very rare: calcification of gallstones; decompensation of liver cirrhosis (during the treatment of advanced stages of PBC), which partially regressed upon discontinuation of treatment.

Skin and subcutaneous tissue disorders:
Very rarely: 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

[To be completed nationally]

4.9 Overdose

Diarrhoea may occur in the event of overdose. In general, other symptoms of overdose are unlikely, as the absorption of this medicinal product decreases with increasing dose and therefore more is excreted with the faeces.

No specific measures are needed and the consequences of diarrhoea must be treated symptomatically with restoration of the fluid and electrolyte balance.

Additional information on special populations
Long-term use of high this medicinal product doses (28-30 mg/kg/day) in patients with primary sclerosing cholangitis (off-label use) was associated with an increase in severe adverse reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: bile therapy, bile acid and derivatives, ATC code: A05AA02

Bile acids are the most important components of bile and play a role in stimulating bile production. Bile acids are also important to keep cholesterol dissolved in bile. In healthy individuals, the ratio between concentrations of cholesterol and bile acids in the bile is such that cholesterol is kept dissolved for most of the day. Thus, no gallstones can form (bile is non-lithogenic). In patients with cholesterol stones in the gallbladder, this ratio is altered and the bile is supersaturated with cholesterol (bile is lithogenic). After some time, this may cause precipitation of cholesterol crystals and the formation of gallstones. This medicinal product can convert lithogenic bile into non-lithogenic bile and also gradually dissolve cholesterol gallstones.

Studies into the effect of this medicinal product on cholestasis in patients with impaired biliary drainage and on clinical symptoms in patients with biliary cirrhosis and cystic fibrosis have shown a rapid decline in cholestatic symptoms in the blood (as measured by increased levels of alkaline phosphatase (AP), gamma-GT and bilirubin) and pruritus, as well as decreased fatigue in most patients.

Paediatric population
Cystic fibrosis
From clinical reports, long-term experience of more than 10 years is available on this medicinal product treatment in paediatric patients with hepatobiliary disorders as a result of cystic fibrosis (CFAHD). It has been demonstrated that treatment with this medicinal product can decrease bile duct proliferation, halt

progression of histological damage and even reverse hepatobiliary changes, when it is given at early stage of CFAHD. Treatment with this medicinal product must be initiated as soon as the diagnosis of CFAHD is made, in order to optimise the effect of treatment.

5.2 Pharmacokinetic properties

Absorption
About 60-80 % of orally administered ursodeoxycholic acid is rapidly absorbed in jejunum and in upper ileum by passive diffusion and in terminal ileum by active transport.

Distribution
Following absorption, ursodeoxycholic acid passes into the liver (there is a considerable "first-pass-effect"), where it is conjugated with glycine or taurine and subsequently excreted into the biliary tract. Only a small proportion of ursodeoxycholic acid is found in the systemic circulation and this is renally excreted.
After repeated dosing, the ursodeoxycholic acid concentration in bile reaches steady state after about 3 weeks: however, the total concentration of ursodeoxycholic acid is never any higher than about 60 % of the total bile acid concentration in bile, even at high dosages.

Biotransformation and elimination
With the exception of conjugation, ursodeoxycholic acid is not metabolised. However, a small amount of orally administered ursodeoxycholic acid undergoes bacterial conversion to 7-keto-lithocholic acid or lithocholic acid after each enterohepatic circulation, while bacterial deconjugation in the duodenum also takes place.
Since ursodeoxycholic acid, 7-keto-lithocholic acid and lithocholic acid are relatively poorly soluble in water, a large amount is excreted via the bile in the faeces. Absorbed ursodeoxycholic acid is reconjugated by the liver; 80 % of the lithocholic acid produced in the duodenum is excreted in the faeces, but the remaining 20 % is sulphated following absorption by the liver to insoluble lithocholyl conjugates, which are then excreted via the bile and faeces. Absorbed 7-keto-lithocholic acid is reduced to chenodeoxycholic acid in the liver.

Lithocholic acid can cause cholestatic liver damage when the liver is not able to sulphate lithocholic acid. Although a reduced capacity to sulphate lithocholic acid in the liver has been found in some patients, there is provisionally no clinical evidence to suggest that cholestatic liver damage can be associated with ursodeoxycholic acid therapy.

Upon discontinuation of therapy with ursodeoxycholic acid, the concentration of ursodeoxycholic acid in bile after 1 week rapidly declines to 5-10 % of the steady-state concentration.

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential.

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

Chronic toxicity
Subchronic toxicity studies in monkeys revealed hepatotoxic effects in the groups treated with higher dosages. These effects concerned both functional changes (such as liver enzyme changes) and morphological changes, such as bile duct proliferation, portal inflammation 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 degraded. Clinical experience confirms that the described hepatotoxic effects are of no apparent relevance in humans.

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.

Reproductive toxicity
In studies with rats, tail malformations occurred at a high dosage of 2000 mg/kg of ursodeoxycholic acid. In rabbits, no teratogenic effects were found, although embryotoxic effects were observed from a dose of 100 mg/kg of body weight. This medicinal product had no effect on fertility in rats and had no influence on peri- and post-natal development of the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch
Silicon dioxide (E 551)
Magnesium stearate (E 470B)

Hard gelatin capsule
Body and cap composition
Titanium dioxide (E 171)
Gelatin (E 441)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 30 °C.
Store in the original packaging material in order to protect from moisture.

6.5 Nature and contents of container

The capsules are packed in PVC/aluminium blisters.
10 capsules per blister. 5, 6 or 10 blisters (50, 60 or 100 capsules) are packed per cardboard box.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

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Date of authorisation: 17.12.2020

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10/2020