SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ursodeoxycholic acid Orion 250 mg capsules, hard

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 (capsule)

White hard gelatin capsule, approximately 21.7 mm x7.64 mm in size, containing white or almost white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

For the dissolution of cholesterol gallstones in the gall bladder. The gallstones should be X-ray negative and have a diameter less than 15 mm. The gall bladder must be functioning despite the gallstone(s).

Primary biliary cirrhosis (PBC) stages I–III.

Paediatric population
Hepatobiliar disorder associated with cystic fibrosis in children aged 6 years to less than 18 years.

4.2 Posology and method of administration

Posology

For the dissolution of symptomatic X-ray negative gallstones with or without prior extracorporeal shockwave lithotripsy
The daily dose depends on body weight and ranges from 10–12 mg/kg body weight a day divided in two doses.

Treatment of gallstones using ursodeoxycholic acid requires a functioning gallbladder.

The time required for dissolution of gallstones is generally 6–24 months. If the size of the gall stones is not reduced within 12 months, treatment should be ended.

Treatment of Primary biliary cirrhosis (PBC)
The daily dose depends on body weight, and ranges from 12–16 mg ursodeoxycholic acid/kg of body weight.

For the first 3 months of treatment, Ursodeoxycholic acid Orion should be taken divided over the day. With improvement of the liver values the daily dose may be taken once daily, preferably in the evening.

Body weight (kg)	Daily dose (mg/kg body weight)	Hard capsules			
		Dosage for the first 3 months			Dosage after the first 3 months
		Morning	Mid-day	Evening	Evening (1 x daily)
47–62	12–16	250 mg	250 mg	250 mg	750 mg
63–78	13–16	250 mg	250 mg	500 mg	1000 mg
79–93	13–16	250 mg	500 mg	500 mg	1250 mg
94–109	14–16	500 mg	500 mg	500 mg	1500 mg
Over 110		500 mg	500 mg	750 mg	1750 mg

Method of administration

The capsules should be swallowed whole with some liquid. Care should be taken to ensure that they are taken regularly. If, due to the size of the capsule, the patient has difficulty swallowing, the capsule may, if necessary, be opened and the contents added to yoghurt, for example.

The use of ursodeoxycholic acid in primary biliary cirrhosis may be continued indefinitely.

In rare cases the clinical symptoms may worsen at the beginning of treatment, e.g. increased itching. Should this occur, therapy should be continued with one 250 mg capsule daily, and the therapy gradually increased (increase of the daily dose weekly by one 250 mg capsule) until the dose indicated in the respective dosage regimen is reached again.

Paediatric population
Children with cystic fibrosis aged 6 years to less than 18 years:
20 mg/kg/day in 2–3 divided doses, with a further increase to 30 mg/kg/day if necessary.

For doses below 250 mg alternative formulations containing ursodeoxycholic acid in solution are available.

4.3 Contraindications

Ursodeoxycholic acid should not be used in patients with:
- Hypersensitivity to the active substance, other bile acids or to any of the excipients listed in section 6.1
- Acute inflammation of the gall bladder or the biliary tract
- Occlusion of the biliary tract (occlusion of the common bile duct or a cystic duct)
- Frequent episodes of biliary colic
- Radio-opaque calcified gallstones
- Impaired contractility of the gall bladder.

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 should be taken under medical supervision.

During the first 3 months of treatment, liver function parameters ASAT (SGOT), ALAT (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 cirrhosis, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with late stage primary biliary cirrhosis.

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, ursodeoxycholic acid should not be used.

Female patients taking ursodeoxycholic acid in order to dissolve gallstones should use effective non-hormonal contraceptives as hormonal oral-contraceptives may increase biliary lithiasis (see sections 4.5 and 4.6).

When used for treatment of late 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 rare cases in patients with primary biliary cirrhosis the clinical symptoms may worsen at the beginning of treatment, e.g. increased itching. Should this occur, therapy should be continued with one 250 mg capsule daily, and the therapy gradually increased to the recommended daily dose, as described in section 4.2.

If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued.

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 affect the absorption of ciclosporin from the intestine. In patients receiving ciclosporin treatment, blood concentrations of this substance should therefore be controlled and the ciclosporin dose 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 certain rare cases ursodeoxycholic acid can reduce the absorption of ciprofloxacin.

Ursodeoxycholic acid has been shown to reduce the plasma peak concentrations C_{max} 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 two interactions in addition to shown *in vitro* interaction could be explained by enzyme induction with CYP3A4. However, no induction was observed in a well-designed interaction study with budesonide.

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

A clinical study on healthy volunteers with concomitant use of ursodeoxycholic acid (500 mg/day) and rosuvastatin (20 mg/day) resulted in increased plasma levels of rosuvastatin. The clinical relevance of this interaction and even the interactions concerning other statins are unknown.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data on the use of ursodeoxycholic acid, particularly in the first trimester of pregnancy. Animal studies have provided evidence of a teratogenic effect during the early phase of gestation (see section 5.3). Ursodeoxycholic acid must not be used during pregnancy unless clearly necessary. Women of childbearing potential should be treated only if they use reliable contraception: non-hormonal contraceptives or low-oestrogen oral contraceptives are recommended. However, in patients taking ursodeoxycholic acid 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
It is not known whether ursodeoxycholic acid passes into breast milk. Passage of ursodeoxycholic acid has not been investigated in animal studies. The mothers need for treatment with ursodeoxycholic acid and the benefit on breastfeeding should be weighed against the possible risk for the infant.

Fertility
Animal studies have not shown any effect of ursodeoxycholic acid on fertility (see section 5.3). Human data on the effect of ursodeoxycholic acid treatment on fertility is missing.

4.7 Effects on ability to drive and use machines

Ursodeoxycholic acid Orion 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 (< 1/10,000)
Not known (cannot be estimated from the available data)

Gastrointestinal disorders
Common: pale 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 after the treatment was discontinued.

Skin and subcutaneous 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 national reporting system listed in Appendix V.

4.9 Overdose

Diarrhoea 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.

No specific counter-measures are necessary and the consequences of diarrhoea should be treated symptomatically with restoration of fluid and electrolyte balance.

Further information regarding certain populations:
In patients with primary sclerosing cholangitis treated with high doses of ursodeoxycholic acid (28–30 mg/kg/day) during longer periods (off-label use), a higher degree of serious undesirable effects have been observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bile acids and derivatives, ATC code: A05AA02

Ursodeoxycholic acid is a hydrophilic bile acid which is part of human bile in low concentration.

In patients with X-ray negative gallstones the addition of ursodeoxycholic acid increases the solubility of cholesterol in bile.
This is achieved through an increase of both the amount of ursodeoxycholic acid in the bile and the total bile volume. Furthermore, ursodeoxycholic acid decreases the intestinal absorption of cholesterol.

In treatment of patients with primary biliary cirrhosis several different mechanisms have been shown. A change in the composition of the bile with a reduction of toxic, endogenous, mainly lipophilic bile acids and an increase in ursodeoxycholic acid are considered to be of largest importance. In addition the flow of bile is stimulated, which results in a faster conversion of the bile acids. The intestinal post-absorption of e.g. cholic acid and other bile acid metabolites are reduced. *In vitro* ursodeoxycholic acid also has a direct protective effect on hepatocytes.

Paediatric population
Cystic fibrosis
From clinical reports long-term experience up to 10 years and more is available with ursodeoxycholic acid treatment in paediatric patients suffering from cystic fibrosis associated hepatobiliary disorders (CFAHD). There is evidence that treatment with ursodeoxycholic acid 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 should be started as soon as the diagnosis of CFAHD is made in order to optimize treatment effectiveness.

5.2 Pharmacokinetic properties

Orally administered ursodeoxycholic acid is quickly absorbed through passive transport in the jejunum and the upper part of ileum in the small intestines and by active transport in the lower part of ileum in the small intestines.

The degree of absorption is dose-dependent and decreases with increasing doses. After absorption the bile acid is almost completely conjugated with the amino acids glycine and taurin in the liver and is then excreted with the bile. First pass metabolism in the liver is in the interval of 50–75 %.

Depending on the daily dose and the underlying disease or the condition of the liver the more hydrophilic ursodeoxycholic acid is accumulated in bile. Concomitantly a decrease in other more lipophilic bile acids has been observed.

Intestinal bacteria impact the incomplete degradation to 7-ketolithocholic acid and lithocholic acid.

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on single and repeated dose toxicity, genotoxicity and carcinogenic potential. Hepatotoxic effects observed in monkeys at high ursodeoxycholic acid doses were most likely due to the metabolite lithocholic acid, which in monkeys, unlike humans, is not detoxified (see section 5.2).
Clinical experience of the therapeutic indications indicates that the hepatotoxic effects are not relevant in humans.

Reproductive studies in animals have revealed embryonic effects of ursodeoxycholic acid in rabbits (from a dose of 100 mg/kg) and teratogenic effects in rats at a dose of 2000 mg/kg. Fertility and peri-/postnatal development in the offspring are not affected in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content:
Maize starch
Silica, colloidal hydrated
Magnesium stearate

Capsule shell:
Titanium dioxide (E171)
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 30 ºC. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

PVC/aluminium blister: 25, 50, 75 and 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2017-08-16

10. DATE OF REVISION OF THE TEXT

30.5.2018