Natrapharm

URSODEOXYCHOLIC ACID

ProUrsan®

250 mg Hard capsule
Bile acid and derivative

1. NAME OF THE MEDICINAL PRODUCT
URSODEOXYCHOLIC ACID (ProUrsan®)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each hard capsule contains 250 mg ursodeoxycholic acid (UDCA) as the active ingredient.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Hard capsule.
White, hard gelatin capsules containing white or almost white powder.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Dissolution of cholesterol gallstones in patients with a high risk for surgery and in patients after lithotripsy. A successful treatment requires a functioning gallbladder and presence of pure radiolucent cholesterol gallstones, which do not exceed 1.5 cm in diameter.
Primary biliary cirrhosis stage I and II.
Primary sclerosing cholangitis.
Hepatitis of various aetiologies with cholestatic syndrome.
Reactive gastritis in duodenogastric reflux.

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
Adults
Dissolution of cholesterol gallstones
The recommended dose in adult patients is 2 to 5 capsules daily dependent on the body weight (10 mg/kg/day). The total daily dose should be administered as one single dose, in the evening before going to bed. ProUrsan® needs to be taken regularly.

Body weight	Ursodeoxycholic acid	Number of capsules
Up to 60 kg	500 mg	2
61-80 kg	750 mg	3
81-100 kg	1,000 mg	4
Over 100 kg	1,250 mg	5

The duration and efficacy of treatment are dependent on the size of gallstones and compliance of patient and it usually lasts from 6 to 24 months. If no reduction of the size of gallstones occurs within one year of treatment, it is recommended not to continue the treatment. During the first 3 months of treatment it is necessary to regularly monitor serum aminotransferases in regular 4-week intervals. If abnormal values are found, it is recommended to temporarily reduce ProUrsan® dosage. Dissolution of gallstones has to be ultrasonically monitored at least in 6-month intervals. After the gallstones are dissolved, it is recommended to continue the treatment for another 3 months to ensure total dissolution of gallstones.
Primary biliary cirrhosis stage I and II and other conditions associated with intrahepatic cholestasis
The daily dose depends on the body weight and usually is 10–15 mg/kg/day (i.e. 2–6 capsules) taken in 2–3 divided doses.

Reactive gastritis in duodenogastric reflux
The recommended dose is 1 capsule (250 mg) daily, administered in the evening before going to bed. The recommended duration of ProUrsan® treatment in this indication is 10–14 days.
Dosage regimen in children over the age of 2 years is individual. The usual recommended dose is 10–20 mg/kg/day. Slightly increased dose is necessary to compensate for reduced intestinal absorption. A different drug form is suitable for children younger than 6 years.

Paediatric population
Children and adolescents with cystic fibrosis aged 6 years to 18 years
20 mg/kg/day should be administered in 2 to 3 divided doses, with a further increase to 30 mg/kg/day if necessary.
Method of administration
The capsules should be swallowed whole and not chewed, with a sufficient amount of fluids.

4.3 Contraindications
– Hypersensitivity to the active substance or to any of the excipients;
– Acute inflammation of the gallbladder or bile ducts;
– Occlusion of extrahepatic bile ducts (choledochus duct or cystic duct);
– Frequent episodes of biliary colics;
– Radiopaque calcified gallstones;
– Impaired contractility of the gallbladder.
Paediatric population
Unsuccessful portoenterostomy or children with biliary atresia without good bile flow.

4.4 Special warnings and precautions for use
ProUrsan® should be administered under medical supervision. During the treatment, it is necessary to monitor liver enzyme levels (AST, ALT, γ-GT): during the first 3 months of treatment, they should be monitored every 4 weeks, thereafter every 3 months. Besides determining whether patients treated for primary biliary cirrhosis respond to the treatment or not, this monitoring could allow timely detection of a potential risk of hepatic damage, especially in patients with primary biliary cirrhosis in an advanced stage.
If used for dissolution of cholesterol gallstones:
In order to assess therapeutic progress and for timely detection of any calcification of the gallstones, oral cholecystography with radiographs in standing and supine positions or ultrasound control should be performed 6–10 months after the beginning of treatment (depending on stone size).
The product should not be used if the gallbladder cannot be imagined using radiography and in the case of calcification of the gallstones.
Female patients using ProUrsan® for dissolution of gallstones should use an efficient non-hormonal contraception method as hormonal anticonception may increase the risk of biliary lithiasis.
If used for the treatment of primary biliary cholangitis in an advanced stage:
Decompensation of liver cirrhosis was observed in very rare cases, which partially subsided after discontinuation of the therapy.
In rare cases, clinical symptoms of the disease may worsen in patients with PBC, for example, the pruritus may worsen. In such a case the ProUrsan® dose should be reduced to one 250 mg capsule of ProUrsan® daily and then the dose should be gradually increased again by one capsule weekly until the originally prescribed dose is reached.
If diarrhoea occurs, the dose must be reduced. If diarrhoea persists, the therapy needs to be stopped.

Paediatric population
The product is not suitable for children younger than 6 years given the strength of the capsule.

4.5 Interaction with other medicinal products and other forms of interaction
Ursodeoxycholic Acid (ProUrsan®) should not be administered concomitantly with cholestyramine, 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 active substances be necessary, it must be taken at least 2 hours before or after Ursodeoxycholic Acid (ProUrsan®).
Ursodeoxycholic Acid (ProUrsan®) can affect the absorption of ciclosporin from the intestine. In patients concurrently receiving this substance, concentrations of cyclosporine should therefore be checked and its dose adjusted if necessary.
In sporadic cases, Ursodeoxycholic Acid (ProUrsan®) can reduce the absorption of ciprofloxacin.
In a clinical study in healthy volunteers concomitant use of UDCA (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.
The ursodeoxycholic acid was demonstrated to decrease the maximum plasma concentration (Cmax) and the area under the curve (AUC) of nitrendipine, a calcium antagonist in healthy volunteers. It is recommended to carefully monitor the result of concurrent administration of nitrendipine and ursodeoxycholic acid. The nitrendipine dose may need to be increased. A decreased therapeutic effect of dapsone was observed. This observation, together with *in vitro* findings, indicated the potential of ursodeoxycholic acid to induce P450 3A cytochrome. However, no induction was observed in a well designed study of an interaction with budesonide, a known P450 3A cytochrome substrate.
Oestrogenic hormones 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 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 that the growth and development of the baby may be affected. The patient should not take Ursodeoxycholic acid (ProUrsan®) 250 mg capsules during pregnancy unless the doctor thinks it is absolutely necessary.
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 Ursodeoxycholic Acid (ProUrsan®) 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.
Breast-feeding
There are only a few documented cases of Ursodeoxycholic acid (ProUrsan®) use in breast-feeding women. Levels of Ursodeoxycholic acid (ProUrsan®) in milk are very low and probably no adverse reactions will occur 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 (< 1/10,000), not known (cannot be estimated from available data).
Gastrointestinal disorders
Common: Rather loose stools or diarrhoea were observed in clinical studies during the therapy.
Very rare: Severe right upper abdominal pain (in patients with primary biliary cirrhosis).
Hepatobiliary disorders
Very rare: Calcification of gallstones, decompensation of liver cirrhosis (in patients with primary biliary cirrhosis in an advanced stage), which partially subsided after the treatment was discontinued.
Skin and subcutaneous tissue disorders
Very rare: Urticaria (mainly at the beginning of the therapy).

4.9 Overdose
Diarrhoea may occur in overdose with UDCA. In this case, the dose must be reduced, and if diarrhoea persist, the treatment must be discontinued.
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. If diarrhoeic stools occur, these should be treated symptomatically with fluids and electrolytes.
Other information for special patient groups
Long-term treatment with high doses of UDCA (28–30 mg/kg/day) in patients with primary sclerosing cholangitis has been associated with an increased incidence of serious adverse reactions.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Medicinal products for the therapy of gallbladder diseases; bile acids preparations. ATC Code: A05AA02.
Ursodeoxycholic acid (UDCA) is an endogenous tertiary bile acid which occurs in human bile in small amounts. It is synthesized in the liver via 7-ketolithocholic acid, which is a product of bacterial oxidation of chenodeoxycholic acid (CDC). UDCA is more hydrophilic and almost non-toxic in comparison with other bile acids.
After oral administration, UDCA inhibits absorption of cholesterol from the intestine, reduces cholesterol synthesis in the liver and reduces secretion of endogenous cholesterol into the bile. The gradual dissolution of cholesterol gallstones is probably caused by dispersing the cholesterol and forming liquid crystals.
In cholestasis and reflux gastritis, the beneficial effect of ursodeoxycholic acid is given by a change of the ratios of lipophilic bile acids and hydrophilic UDCA concentrations, which is due to the supply of exogenous UDCA and the formation of non-toxic mixed micelles. UDCA forms mixed micelles with apolar bile acid CDC. In these micelles, CDC represents the apolar core, and UDCA the envelope. Thus, toxic CDC is trapped inside the micelle, and the toxic and membrane-damaging effect of reflux fluid in the gastric juice is thus suppressed.
Due to UDCA polar nature, molecular pairs are moreover formed, which can be incorporated into the cellular membranes rich in phospholipids. As a result, the cellular membrane is stabilized and it is no longer susceptible to the aggressive effects of cytotoxic micelles.
This effect is mediated also through UDCA cytoprotective and immunological action.
There are three principal mechanisms of UDCA action in primary biliary cirrhosis:
– Displacement of apolar bile acids (formation of non-toxic mixed micelles)
– Stabilization of the cellular membrane
– Immunological action.
Paediatric population
Cystic fibrosis
From clinical studies up to 10 years and more, experience is available with UDCA treatment in paediatric patients suffering from hepatobiliary disorders associated with cystic fibrosis (CFAHD). There is evidence that treatment with UDCA can decrease bile duct proliferation, halt progression of histological damage and even reverse hepatobiliary changes if given in early stages of CFAHD. Treatment with UDCA should be started as soon as the diagnosis of CFAHD is made in order to optimize treatment effectiveness.

5.2 Pharmacokinetic properties
Absorption
When given orally, ursodeoxycholic acid is rapidly absorbed in jejunum and in the upper part of ileum by passive, and in the terminal ileum by active transport. Peak plasma concentration is reached 30–60 minutes after administration.
Biotransformation and elimination
After absorption, this bile acid is metabolized by almost complete conjugation with the amino acids glycine and taurine in the liver, and subsequently it is excreted from the liver into the bile.
In the intestine, ursodeoxycholic acid is deconjugated and dehydroxylated to lithocholic acid. Through enterohepatic circulation, this acid is transported to the liver and there it is transformed back to chenodeoxycholic acid and UDCA. With respect to the above-mentioned transformation it seems that during the treatment with UDCA, the amount of lithocholic acid is important. Lithocholic acid is partially absorbed and bound to sulphate anion and further conjugated with glycine and taurine and excreted in the bile. These derivatives are only to a small extent absorbed in the intestine and they are excreted in the faeces, which represents an effective mechanism of elimination of this toxic bile acid.

5.3 Preclinical safety data
Acute toxicity
Mean LD_{50} values are > 5 g/kg in rats, > 10 g/kg in mice, and > 10 g/kg in dogs.
Subacute toxicity
In the first part, the rats received an oral dose ranging from 0.5 g/kg to 4 g/kg for 5 weeks. No gross dose-dependent pathological or histopathological changes have been observed.
In the second part, the rats received parenteral doses of 62.5 mg/kg, 125 mg/kg, 250 mg/kg and 500 mg/kg.
Histopathological findings (liver necrosis, cholangitis, cell proliferation, proliferation of connective fibres and small biliary ducts, renal abscess) were observed at doses of 125 mg/kg and higher.

Mutagenicity
Mutagenic potential are tested using the following tests: reverse mutation test, micronucleus test; chromosomal aberration test, mouse lymphoma mutation test.
The results showed no mutagenic effect of ursodeoxycholic acid.

Carcinogenicity
In two two-year studies in mice, tests were carried out with doses of 25, 150 and 1,000 mg/kg/day.
No changes in tumour incidence were observed at doses up to 150 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Maize starch
Maize starch, pregelatinised
Silica colloidal anhydrous
Magnesium stearate
Titanium dioxide
Gelatin

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
36 months

6.4 Storage condition
Store at temperatures not exceeding 30°C.
Keep out of reach of children.

6.5 Nature and contents of container
PVC/PVdC and Al blister, carton.
Pack size: 30, 50 or 100 capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
No special requirements.

www.fda.gov.ph

For suspected adverse drug reaction, report to the FDA:
Seek medical attention immediately at the first sign of any adverse drug reaction.

7. MARKETING AUTHORISATION HOLDER
Imported and Distributed by:
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The Patriot Bldg., South Luzon, Express Way, Parañaque, Metro Manila, Philippines

Manufactured by:
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