

Ursodeoxycholic Acid

UDCARE 250 250 mg Capsule Bile Acid and Derivative

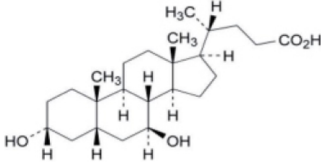


FORMULATION

Each hard gelatin capsule contains:
Ursodeoxycholic Acid BP.....250 mg
Excipientq.s.

DESCRIPTION

Ursodeoxycholic Acid (UDCARE 250) capsule are indicated in the treatment of primary biliary cirrhosis (PBC) and for the dissolution of small to medium sized radiolucent, cholesterol-rich gall-stones in patients with a functioning gall bladder. Its chemical name is cholan-24-oi acid, 3,7-dihydroxy-, (3 α ,5 β ,7 β). The molecular formula is C₂₄H₄₀O₄ with molecular weight of 392.6 g/mol. Its structural formula is:



Ursodeoxycholic Acid (UDCARE 250) represents a white or almost white powder. It is practically insoluble in water, freely soluble in ethanol 96%, slightly soluble in acetone, practically insoluble in methylene chloride.

Ursodeoxycholic Acid (UDCARE 250) hard gelatin capsule is red coloured cap and body, hard gelatin capsule size “1” filled with white powder. It contains Maize starch BP, MCCP-PH102 BP, Isopropyl Alcohol BP, PVP K 30 BP, Sodium Lauryl sulfate BP, Colloidal Anhydrous Silica BP, Purified Talc BP, Magnesium Stearate BP, Hard Gelatin Capsule Shell “1” Color RD/RD IH.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group/ATC code
Group: Bile acid preparations
Code: A05AA02 and A05B

Ursodeoxycholic Acid (UDCARE 250) is a bile acid which effects a reduction in cholesterol in biliary fluid primarily by dispersing the cholesterol and forming a liquid-crystal phase.

Paediatric population

Cystic fibrosis.

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

Pharmacokinetic properties

Ursodeoxycholic Acid (UDCARE 250) occurs naturally in the body. When given orally it is rapidly and completely absorbed. It is 96-98% bound to plasma proteins and efficiently extracted by the liver and excreted in the bile as glycine and taurine conjugates. In the intestine some of the conjugates are deconjugated and reabsorbed. The conjugates may also be dehydroxylated to lithocholic acid, part of which is absorbed, sulphated by the liver and excreted via the biliary tract.

Preclinical safety data

a) Acute toxicity

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

b) Chronic toxicity

Subchronic toxicity studies in monkeys showed hepatotoxic effects in the groups given high doses, including functional changes (e.g. liver enzyme changes) and morphological changes such as bile duct proliferation, portal inflammatory foci and hepatocellular necrosis. These toxic effects are most likely attributable to lithocholic acid, a metabolite of UDCA, which in monkeys – unlike humans – is not detoxified. Clinical experience confirms that the described hepatotoxic effects are of no apparent relevance in humans.

c) Carcinogenic and mutagenic potential

Long-term studies in mice and rats revealed no evidence of Ursodeoxycholic Acid (UDCARE 250) having carcinogenic potential.

In vitro and in vivo genetic toxicology tests with UDCA were negative.

The tests with Ursodeoxycholic Acid (UDCARE 250) revealed no relevant evidence of a mutagenic effect.

d) Toxicity to reproduction

In studies in rats, tail malformations occurred after a dose of 2000 mg of ursodeoxycholic acid per kg of body weight. In rabbits, no teratogenic effects were found, although there were embryotoxic effects (from a dose of 100 mg per kg of body weight). Ursodeoxycholic Acid (UDCARE 250) had no effect on fertility in rats and did not affect peri-/post-natal development of the offspring.

INDICATIONS

Ursodeoxycholic acid is indicated in the treatment of primary biliary cirrhosis (PBC) and for the dissolution of radiolucent gallstones in patients with a functioning gall bladder.

Paediatric population

Hepatobiliary disorders associated with cystic fibrosis in children aged 6 to 18 years

DOSAGE AND ADMINISTRATION

There are no age restrictions on the use of Ursodeoxycholic Acid (UDCARE 250) 250 mg hard capsules in the treatment of PBC and for the dissolution of radiolucent gallstones. For patients weighing less than 47 kg or patients who are unable to swallow Ursodeoxycholic acid capsules, Ursodeoxycholic acid suspension is available.

The following daily dose is recommended for the various indications:

Treatment of Primary biliary cirrhosis (PBC):

The daily dose depends on body weight, and ranges from 3 to 7 capsules (14 $\pm$ 2 mg ursodeoxycholic acid per kg of body weight).

For the first 3 months of treatment, Ursodeoxycholic acid should be taken divided over the day. With improvement of the liver values

the daily dose may be taken once daily in the evening

Body Weight (kg)	Daily Dose (mg/kg BW)	URSODEOXYCHOLIC ACID 250 mg Capsule			
		Dosage for the first 3 months			Subsequently
		Morning	Midday	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

The capsules should be swallowed whole with water. Care should be taken to ensure that they are taken regularly.

The use of Ursodeoxycholic acid capsules in PBC may be continued indefinitely.

Dissolution of Gallstones:

Adults: The usual dose is 8–12 mg/kg/day to be taken in the evening, e.g. 750mg, daily in the evening. The time required for dissolution of gallstones is likely to range from 6 to 24 months depending on stone size and composition. Follow-up cholecystograms or ultrasound investigation may be useful at 6 month intervals until the gallstones have disappeared. Treatment should be continued until 2 successive cholecystograms and/or ultrasound investigations 4-12 weeks apart have failed to demonstrate gallstones. This is because these techniques do not permit reliable visualization of stones less than 2mm in diameter. The likelihood of recurrence of gallstones after dissolution by bile acid treatment has been estimated as up to 50% at 5 years. The efficiency of Ursodeoxycholic Acid (UDCARE 250) in treating radio-opaque or partially radio-opaque gallstones has not been tested but these are generally thought to be less soluble than radiolucent stones. Non-cholesterol stones account for 10-15% of radiolucent stones and may not be dissolved by bile acids.

Older people

There is no evidence to suggest that any alteration in the adult dose is needed but the relevant precautions should be taken into account.

Paediatric population

Cholesterol rich gallstones and PBC are very rare in children but when they occur, dosage should be related to body weight. There are no adequate data on the efficacy and safety in this population.

Hepatobiliary disorders associated with cystic fibrosis:

Paediatric population

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

Body Weight (kg)	Daily Dose (mg/kg BW)	URSODEOXYCHOLIC ACID 250 mg Capsule		
		Morning	Midday	Evening
20-29	17-25	250 mg	--	250 mg
30-39	19-25	250 mg	250 mg	250 mg
40-49	20-25	250 mg	250 mg	500 mg
50-59	21-25	250 mg	500 mg	500 mg
60-69	22-25	500 mg	500 mg	500 mg
70-79	22-25	500 mg	500 mg	750 mg
80-89	22-25	500 mg	750 mg	750 mg
90-99	23-25	750 mg	750 mg	750 mg
100-109	23-25	750 mg	750 mg	1000 mg
Over 110		750 mg	1000 mg	1000 mg

CONTRAINDICATIONS

Ursodeoxycholic Acid (UDCARE 250) 250 mg hard capsules should not be used in patients with:

- Hypersensitivity to bile acids or to any of the excipients of the formulation
- 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

When used in hepatobiliary disorders associated with cystic fibrosis in children aged 6 to 18 years.

- Unsuccessful portoenterostomy or without recovery of good bile flow in children with biliary atresia.

SPECIAL WARNINGS AND PRECAUTIONS

Ursodeoxycholic Acid (UDCARE 250) capsules 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 section 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. the itching may increase. Should this occur, therapy should be reduced to 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.

FERTILITY, PREGNANCY AND LACTATION

Animal studies did not show an influence of Ursodeoxycholic Acid (UDCARE 250) on fertility (see section 5.3). Human data on fertility effects following treatment with UDCA are not available.

Pregnancy

There are no or limited amounts of data from the use of Ursodeoxycholic Acid (UDCARE 250) in pregnant women. Studies in animals have shown reproductive toxicity during the early phase of gestation (see section 5.3). Ursodeoxycholic Acid (UDCARE 250) capsules must not be used during pregnancy unless clearly necessary.

Women of childbearing potential

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 (UDCARE 250) 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 breast-feeding women, milk levels of Ursodeoxycholic Acid (UDCARE 250) are very low and probably no adverse reactions are to be expected in breast-feed infants.

DRUG INTERACTIONS

Interaction with other medicinal products and other forms of interaction

Ursodeoxycholic Acid (UDCARE 250) 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 (UDCARE 250) 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. Due to the effect of UDCA 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 (UDCARE 250) can reduce the absorption of ciprofloxacin.

Ursodeoxycholic Acid (UDCARE 250) 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 UDCA is recommended. An increase of dose 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 increase hepatic cholesterol secretion and may encourage 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 UDCA (500 mg/day) and rosuvastatin (20 mg/day) resulted in rather increased plasma levels of rosuvastatin. The clinical relevance of this interaction and even the interactions concerning other statins are unknown.

Effects on ability to drive and use machines

Ursodeoxycholic Acid (UDCARE 250) has no or negligible influence on the ability to drive and use machines.

ADVERSE DRUG REACTION

Undesirable effects

The evaluation of undesirable effects is based on the following frequency data:

Very common ($\geq$ 1/10)

Common ($\geq$ 1/100 to < 1/10)

Uncommon ($\geq$ 1/1,000 to < 1/100)

Rare ($\geq$ 1/10,000 to < 1/1,000)

Very rare (< 1/10,000)

Not known (cannot be estimated from available data)

Gastrointestinal disorders

In clinical trials, reports of pale stools or diarrhoea during Ursodeoxycholic Acid (UDCARE 250) therapy were common.

Very rarely, severe right upper abdominal pain has occurred during the treatment of primary biliary cirrhosis.

Hepatobiliary disorders

During treatment with Ursodeoxycholic Acid (UDCARE 250), calcification of gallstones can occur in very rare cases.

During therapy of the advanced stages of primary biliary cirrhosis, in very rare cases decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.

Skin and subcutaneous disorders:

Very rarely, urticaria can occur.

OVERDOSE AND TREATMENT

Diarrhea may occur in cases of overdose. In general, other symptoms of overdose are unlikely because the absorption of Ursodeoxycholic Acid (UDCARE 250) 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.

Additional information on special populations:

Long-term, high-dose Ursodeoxycholic Acid (UDCARE 250) therapy (28-30 mg/kg/day) in patients with primary sclerosing cholangitis (off-label use) was associated with higher rates of serious adverse events.

AVAILABILITY

Alu/Alu blister Pack of x 10's (Box of 30's).

STORAGE CONDITION

Store at temperatures not exceeding 30°C.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT:

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

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Distributed By:

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