Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ursodeoxycholic Acid 250 mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 250 mg ursodeoxycholic acid (UDCA).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsules, hard.

Hard gelatine capsuleswith white body and cap filled with powder
The length of the capsules are 21.7 ± 0.3 mm

4 CLINICAL PARTICULARS

4.1 Therapeutic 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.

4.2 Posology and method of administration

Posology
There are no age restrictions on the use of Ursodeoxycholic acid 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 ±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 body weight)	Ursodeoxycholic acid 250 mg hard capsules			
		Dosage for the first 3 months			Subsequently
		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

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 visualisation 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 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.

Elderly
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 bodyweight. There are no adequate data on the efficacy and safety in this population.

Hepatobiliary disorders associated with cystic fibrosis:
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 body weight)	Ursodeoxycholic acid 250 mg hard capsules		
		Morning	Mid-day	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
>110		750 mg	1000 mg	1000 mg

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Ursodeoxycholic acid 250 mg hard capsules should not be used in patients with:
- Hypersensitivity to bile acids
- 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.

4.4 Special warnings and precautions for use

Ursodeoxycholic acid 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.

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 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 can reduce the absorption of ciprofloxacin.
Ursodeoxycholic acid has been shown to reduce the plasma peak concentrations Cmax 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.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amounts of data from the use of UDCA in pregnant women. Studies in animals have shown reproductive toxicity during the early phase of gestation (see section 5.3). Ursodeoxycholic acid 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 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 UDCA are very low and probably no adverse reactions are to be expected in breastfed infants.

Fertility
Animal studies did not show an influence of UDCA on fertility (see section 5.3). Human data on fertility effects following treatment with UDCA 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)

System Organ Class	Frequency	Adverse Reaction
Gastrointestinal disorders	Common	pale stools or diarrhea*
	Very rare	severe right upper abdominal pain**
Hepatobiliary disorders	Very rare	calcification of gallstones
		decompensation of hepatic cirrhosis***
Skin and subcutaneous tissue disorders	Very rare	urticaria

*In clinical trials, reports of pale stools or diarrhoea during ursodeoxycholic acid therapy were common.
**Very rarely, severe right upper abdominal pain has occurred during the treatment of primary biliary cirrhosis
***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

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 HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms
Diarrhoea may occur in cases of overdose. In general, other symptoms of overdose are unlikely because the absorption of UDCA decreases with increasing dose and therefore more is excreted with the faeces.

Management
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 UDCA 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 acid preparations, ATC code: A05AA02 and A05B

Mechanism of action
UDCA 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.

5.2 Pharmacokinetic properties

UDCA 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.

5.3 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 UDCA having carcinogenic potential.
In vitro and in vivo genetic toxicology tests with UDCA were negative.
The tests with UDCA 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).
UDCA had no effect on fertility in rats and did not affect peri-/post-natal development of the offspring.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Magnesium stearate
Maize starch
Silica colloidal anhydrous
Capsule shell:
Titanium dioxide (E171)
Gelatin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (PVC/Alu): 25, 50, 60, 75, 100 Hard gelatin capsules with white body and cap filled with powder The length of the capsules is 21.7 ± 0.3 mm. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Amdipharm Limited
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Northwood House, Northwood Crescent
Northwood, Dublin 9
D09 V504, Ireland

8 MARKETING AUTHORISATION NUMBER

PA1142/018/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th February 2016
Date of last renewal: 16th March 2020

10 DATE OF REVISION OF THE TEXT

November 2025