Summary of Product Characteristics

1. Name of the medicinal product

Cholemax suspension

2. Qualitative and quantitative composition

Ursodeoxycholic acid (UDCA) 250 mg / 5 mL

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Oral suspension.

White, homogenous suspension, with strawberry yoghurt odour.

4. Clinical particulars

4.1 Therapeutic indications

- Treatment of primary biliary cholangitis (PBC)
- For the dissolution of radiolucent gallstones in patients with a functioning gall bladder
- Hepatobiliary disorders associated with cystic fibrosis in children aged 1 month to 18 years.

4.2 Posology and method of administration

There are no age restrictions on the use of ursodeoxycholic acid (UDCA) suspension in the treatment of PBC and for the dissolution of radiolucent gallstones. The following daily dose is recommended for the various indications:

<u>For the treatment of primary biliary cholangitis (PBC)</u>

The daily dose depends on body weight, and is approximately 14 ± 2 mg UDCA per kg of body weight.

For the first 3 months of treatment, UDCA suspension should be taken divided over the day. When the liver function parameters improve, the daily dose can be administered once a day in the evening.

Body weight (kg)	Daily dose (mg/kg/BW)	Cups* of UDCA suspension			
		First 3 months			subsequently
		morning	midday	evening	Evening (1xdaily)
8-11	12-16	-	¼	¼	½
12-15	12-16	¼	¼	¼	¾
16-19	13-16	½	-	½	1
20-23	13-15	¼	½	½	1 ¼
24-27	13-16	½	½	½	1 ½
28-31	14-16	¼	½	1	1 ¾
32-39	12-16	½	½	1	2
40-47	13-16	½	1	1	2 ½
48-62	12-16	1	1	1	3
63-80	12-16	1	1	2	4
81-95	13-16	1	2	2	5
96-115	13-16	2	2	2	6
Over 115		2	2	3	7

*One cup (5 ml oral suspension) contains 250 mg of UDCA.

UDCA suspension should be taken in accordance with the dosage regimen given above. The oral suspension must be taken regularly.

The use of UDCA suspension in PBC may be continued indefinitely.

For dissolution of cholesterol gallstones:

Approximately 10 mg of UDCA per kg of body weight daily, equivalent to:

Body weight	Cups*	Eq. to mL
51 to 65 kg	2 ½	12.50
66 to 80 kg	3	15.00
81 to 100 kg	4	20.00
Over 100 kg	5	25.00

*One cup (= 5 ml oral suspension) contains 250 mg of UDCA.

UDCA suspension should be taken in the evening at bedtime. The oral suspension must be taken regularly.

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 months 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 stonesless than 2 mm 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 UDCA 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 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 1 month to 18 years: 20 mg/kg/day in 2-3 divided doses, with a further increase to 30 mg/kg/day if necessary

Very rarely, children under 10 kg body weight are affected. In this case, a commercially available single-use syringe should be used.

(Please note: a syringe is not provided in the pack)

Up to 10 kg body weight: Dosing 20 mg UDCA/kg/day

Measuring device: single-use 2 ml graduated syringe (not provided)

Body weight (kg)	UDCA suspension (mL)	
	Morning	Evening
4	0.8	0.8
4.5	0.9	0.9
5	1.0	1.0
5.5	1.1	1.1
6	1.2	1.2
6.5	1.3	1.3
7	1.4	1.4
7.5	1.5	1.5
8	1.6	1.6
8.5	1.7	1.7
9	1.8	1.8
9.5	1.9	1.9
10	2.0	2.0

More than 10 kg body weight (BW): Dosing 20-25 mg UDCA/kg/day

Measuring device: measuring cup

Body weight (kg)	Daily dose UDCA (mg/kg/BW)	*Cups of UDCA suspension	
		Morning	Evening
11-12	21-23	½	½
13-15	21-24	½	¾
16-18	21-23	¾	¾
19-21	21-23	¾	1
22-23	22-23	1	1
24-26	22-23	1	1 ¼
27-29	22-23	1 ¼	1 ¼
30-32	21-23	1 ¼	1 ½
33-35	21-23	1 ½	1 ½
36-38	21-23	1 ½	1 ¾
39-41	21-22	1 ¾	1 ¾
42-47	20-22	1 ¾	2
48-56	20-23	2 ¼	2 ¼
57-68	20-24	2 ¾	2 ¾
69-81	20-24	3 ¼	3 ¼
82-100	20-24	4	4
>100		4 ½	4 ½

* Conversion table:

	UDCA suspension	UDCA
1 cup	= 5 ml	= 250 mg
¾ cup	= 3.75 ml	=187.5 mg
½ cup	= 2.5 ml	= 125 mg
¼ cup	=1.25 ml	= 62.5 mg

4.3 Contraindications

UDCA suspension should not be used in patients with:

- Acute inflammation of the gall bladder or biliary tract

- Occlusion of the biliary tract (occlusion of the common bile duct or cystic duct)

- Frequent episodes of biliary colic

- Radio-opaque calcified gallstones

- Impaired contractility of the gall bladder

- Hypersensitivity to bile acids or any excipient of the formulation

When used in hepatobiliary disorders associated with cystic fibrosis in children aged 1 month 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

UDCA suspension should be taken under medical supervision.

During the first 3 months of treatment, liver function parameters AST (SGOT), ALT (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 PBC, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advance stage PBC.

When used for treatment of advanced stage of primary biliary cholangitis:

In very rare cases decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.

In patients with PBC, in rare cases the clinical symptoms may worsen at the beginning of treatment, e.g. the itching may increase. In this case the dose of UDCA suspension should be

reduced to 250 mg daily and then gradually increased to the recommended dose described in section 4.2.

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

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, UDCA suspension should not be used.

Female patients taking UDCA for dissolution of gallstones should use an effective non-hormonal method of contraceptive, since hormonal contraceptives may increase biliary lithiasis (see section 4.5 and 4.6)

This medicinal product contains 13 mg sodium per 5 ml of suspension, equivalent to 0.65 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

UDCA suspension should not be administered concomitantly with colestyramine, colestipol or antacids containing aluminium hydroxide and/or smectite (aluminium oxide), because these preparations bind UDCA 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 UDCA suspension.

UDCA suspension 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.

In isolated cases, UDCA suspension 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.

UDCA has been shown to reduce the peak plasma concentrations (Cmax) and 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 in the dose of nitrendipine may be necessary. An interaction with a reduction of the therapeutic effect of dapsone was also reported. These observations, together with in-vitro findings, could indicate a potential for UDCA to induce cytochrome P450 3A enzymes. Induction has, however, not been observed in a well-designed interaction study with budesonide, which is a known cytochrome P450 3A 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 UDCA used for dissolution of gallstones.

4.6 Pregnancy and lactation

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.

Pregnancy

There are no or limited amounts of data on the use of UDCA in pregnant women. Studies in animals have shown reproductive toxicity during the early phase of gestation (see section 5.3).

UDCA suspension must not be used during pregnancy unless clearly 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 UDCA 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

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.

4.7 Effects on ability to drive and use machine

UDCA 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 / Not known (< 1/10,000 / cannot be estimated from available data)	

Gastrointestinal disorders:

In clinical trials, reports of pasty stools or diarrhoea during UDCA therapy were common.

Very rarely, severe right upper abdominal pain has occurred during the treatment of PBC.

Hepatobiliary disorders:

During treatment with UDCA, calcification of gallstones can occur in very rare cases.

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

Skin and subcutaneous tissue disorders:

Very rarely, urticaria can occur.

4.9 Overdose

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.

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/ATC code

Group: Bile Acid Preparation

Code: A05AA02 and A05B

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. UDCA affects the enterohepatic circulation of bile salts by reducing the ileal reabsorption of endogenous more hydrophobic and potentially toxic salts such as cholic and chenodeoxycholic acids.

In-vitro studies show that UDCA has a direct hepatoprotective effect and reduces the hepatotoxicity of hydrophobic bile salts. Immunological effects have also been demonstrated with a reduction in abnormal expression of HLS Class I antigens on hepatocytes as well as suppression of cytokine and interleukin production.

Cystic fibrosis - Paediatric population

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 hepatobiliary 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 optimise 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 UDCA 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

Liquid maltitol, glycerin, xanthan gum, carmellose sodium, citric acid, sodium citrate, sodium chloride, saccharin sodium, xylitol, ammonium glycyrrhizinate, methyl hydroxybenzoate, propyl hydroxybenzoate, strawberry flavor, yoghurt flavor, purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Tentative shelf life 24 months

6.4 Special precautions for storage

Keep in tight container, store below 30 ºC.

Once opened, store in room temperature (<30°C) and use within 4 months.

6.5 Nature and contents of container

- Fill 60, 100, 120, 125, 150, 180, 200, 225, 250, or 300 ml in an amber PET bottle, with a white polypropylene (PP) child-resistant cap containing an internal polyethylene (PE) liner, or with an aluminium screw cap containing an internal polyethylene (PE) liner, and then be packed in a

paper box.

- Fill 60, 100, 120, 125, 150, 180, 200, 225, 250, or 300 ml in an amber glass bottle, with a white polypropylene (PP) child-resistant cap containing an internal polyethylene (PE) liner, or with an aluminium screw cap containing an internal polyethylene (PE) liner, and then be packed in a paper box.

Not all pack sizes may be marketed.

7. Marketing Authorization Holder

Manufactured by

Macrophar Co., Ltd.

Bangkok, Thailand

Distributed by

Macrophar Lab Co., Ltd.

28/8, Soi Pattanakarn 20 Yaek 4, Suan Luang, Bangkok, 10250 Thailand

Tel (662) 314-6671

8. Marketing Authorization Numbers

1A 109/67

9. Date of authorization

October 20, 2024

10. Date of revision of the text

November 19, 2024