MICRO LABS LIMITED, BANGALORE, INDIA			
1	Product Name	Ursodox	Colours Used
2	Strength	250 mg	■ BLACK
3	Component	Leaflet	
4	Category	Export - Philippines	
5	Dimension	120 (L) x 240 (H) mm	
6	Artwork Code	EXG-ML01I-1119/A	
7	Pharma Code	N/A	
8	Reason for Change	New Regulation text	

	Prepared by (DTP)	Checked by (PD)	Approved by			
			Head CQA	Head Production/ Packing (Site)	Head QC (Site)	Head QA (Site)
Sign	Kantharaju L.					
Date	02-11-2021					

Size: 120 (L) x 240 (H) mm
Folding size: 30 x 60 mm
Carton size: 85 x 80 x 65 mm

Front

Back

240 mm

120 mm

120 mm

URSODEOXYCHOLIC ACID

Ursodox

250 mg Capsule
Bile Acid Therapy

PRODUCT NAME: Ursodox

DOSAGE FORM AND STRENGTH: Ursodeoxycholic acid Ph. Eur. 250 mg

PHARMACOLOGIC CATEGORY: Bile acid preparations

PRODUCT DESCRIPTION
Hard gelatin capsule of size "0", with white opaque cap and white opaque body, printed MICRO on cap and MICRO on body with black ink filled with white to off-white powder.

FORMULATION/COMPOSITION:
Each hard gelatin capsule contains:
Ursodeoxycholic acid Ph. Eur……. 250 mg

PHARMACOKINETICS:
Absorption: About 90% of an oral dose absorbed in small intestine. Only small amounts of Ursodeoxycholic acid appear in the systemic circulation.
Distribution & Protein Binding: Following absorption from the GI tract, Ursodeoxycholic acid distributes to the portal vein and undergoes hepatic extraction (about 50% in the absence of liver disease; extent of extraction decreases as severity of liver disease increases) from portal blood by the liver (i.e., there is a large first-pass effect). After drug is conjugated in liver, it is distributed into bile. Ursodeoxycholic acid in bile is concentrated in the gallbladder and distributed into the duodenum in gallbladder bile via the cystic and common ducts by gallbladder contractions stimulated by physiologic responses to eating. The plasma protein binding in healthy individual's ≥70% (as unconjugated Ursodeoxycholic acid)
Metabolism: Ursodeoxycholic acid is conjugated with glycine or taurine in the liver and distributed into bile. Ursodeoxycholic acid conjugates are absorbed into small intestine by passive and active mechanisms. These conjugates may be deconjugated in the ileum by intestinal enzymes (or by bacteria in the small intestine), creating free Ursodeoxycholic acid that can be reabsorbed and deconjugated in the liver. Unabsorbed Ursodeoxycholic acid reaches the colon unchanged, where it is primarily 7-dehydroxylated to form lithocholic acid. Some Ursodeoxycholic acid may be epimerized to form chenodiol, which also undergoes 7-dehydroxylation to form lithocholic acid. A small portion of lithocholic acid is reabsorbed and conjugated in the liver with glycine or taurine, and sulfated at the 3 position. Ursodeoxycholic acid can also be oxidized at the 7-carbon, producing 7-keto-lithocholic acid. Absorbed 7-keto-lithocholic acid is stereo specifically reduced in the liver to chenodiol. A small portion of orally administered Ursodeoxycholic acid undergoes bacterial degradation with each cycle of enterohepatic circulation.
Elimination: It is excreted principally in the feces. Urinary excretion increases with treatment but remains below 1% except in patients with severe cholestatic liver disease. Lithocholic acid formed in the small intestine is primarily (80%) excreted in the feces; the 20% that is absorbed is sulfated at the 3-hydroxyl group in the liver to relatively insoluble lithocholic conjugates, which are then excreted into bile and eliminated in the feces.

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.

DOSAGE AND MODEL ROUTE OF ADMINISTRATION:
There are no age restrictions on the use of Ursodeoxycholic acid 250mg hard capsules. For patients weighing less than 47 kg or patients who are unable to swallow Ursodeoxycholic acid 250mg hard capsules, Ursodeoxycholic acid suspension is available.
The following daily dose is recommended for the various indications:
For 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 250mg hard capsules 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 250mg hard capsules			
		first 3 months			subsequently
		morning	midday	evening	evening (1 x daily)
47 – 62	12 – 16	1	1	1	3
63 – 78	13 – 16	1	1	2	4
79 – 93	13 – 16	1	2	2	5
94 – 109	14 – 16	2	2	2	6
Over 110		2	2	3	7

The capsules should be swallowed whole with some liquid. Care should be taken to ensure that they are taken regularly.
The use of Ursodeoxycholic acid 250mg hard capsules in primary biliary cirrhosis may be continued indefinitely.
In patients with primary biliary cirrhosis, in rare cases the clinical symptoms may worsen at the beginning of treatment, e.g. the itching may increase. Should this occur, therapy should be continued with 1 capsule daily, and the therapy gradually increased (increase of the daily dose weekly by 1 capsule) until the dose indicated in the respective dosage regimen is reached again.
Dissolution of Gallstones:
Adults: The usual dose is 8-12mg/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 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.
Children: Cholesterol rich gallstones are rare in children but when they occur, dosage should be related to bodyweight.

MODE OF ADMINISTRATION
The daily dose depends on body weight, and ranges from 3 to 7. For the first 3 months of treatment.

CONTRAINDICATIONS &PRECAUTION(S), WARNING(S)
Ursodeoxycholic acid 250mg hard capsules 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 a 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

PRECAUTIONS AND WARNINGS:
Ursodeoxycholic acid 250mg hard capsules 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 primary biliary cirrhosis, this monitoring would also enable early detection of potential hepatic deterioration, particularly in patients with advanced 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 visualized (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 visualized on X-ray images, or in cases of calcified gallstones, impaired contractility of the gall bladder or frequent episodes of biliary colic, Ursodeoxycholic acid 250mg hard capsules should not be used.
When used for treatment of advanced stage of primary biliary cirrhosis:
In very rare cases decompensation of hepatic cirrhosis has been observed, which partially regressed after the treatment was discontinued.
If diarrhoea occurs, the dose must be reduced and in cases of persistent diarrhoea, the therapy should be discontinued.

INTERACTIONS:
Ursodeoxycholic acid 250mg hard capsules should not be administered concomitantly with cholestyramine, colestipol or antacids containing aluminum hydroxide and/or smectite (aluminum 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 250mg hard capsules.
Ursodeoxycholic acid 250mg hard capsules can increase 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 Ursodeoxycholic acid 250mg hard capsules 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.
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 Ursodeoxycholic acid to induce cytochrome P450 3A enzymes. Controlled clinical trials have shown, however, that Ursodeoxycholic acid does not have a relevant induction effect on cytochrome P450 3A enzymes.
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.

ADVERSE 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 Ursodeoxycholic acid 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, 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.

STORAGE CONDITION:
Store at temperatures not exceeding 30°C

DOSAGE FORMS AND PACKAGING AVAILABLE:
Ursodeoxycholic acid 250 mg: Alu/PVC Blister Pack of 10's (Box of 100's)

INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL (IF APPLICABLE):
Not Applicable

NAME AND ADDRESS OF MARKETING AUTHORIZATION HOLDER:
Marketing Authorization Holder
Brown & Burk Philippines Inc
U-501, 5/F., SEDCCO 1 Bldg., 120 Rada cor.,
Legaspi Sts., Legaspi Village, Makati City, Philippines

NAME AND ADDRESS OF MANUFACTURER:
MICRO LABS LIMITED
92, Sipcot, Hosur - 635 126,
Tamil Nadu, India

CAUTION STATEMENT:
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 Adverse Drug Reaction.

REGISTRATION NUMBER:
DRP-7697

DATE OF FIRST AUTHORIZATION:
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DATE OF REVISION OF PACKAGE INSERT:
May 2019

EXG-ML01I-1119/A