APPROVED
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INSTRUCTION
for medical use

UKRLIV®

Composition:
active substance: ursodeoxycholic acid;
1 tablet contains 250 mg of ursodeoxycholic acid;
excipients: microcrystalline cellulose, sodium starch glycolate (type A), povidone K-30, magnesium stearate.

Pharmaceutical form. Tablets.
Main physical and chemical properties: white round biconvex tablets, smooth on both sides.

Pharmacotherapeutic group.
Drugs used for treatment of liver and biliary tract. Drugs used in case of biliary pathology. ATC Code A05A A02.
Drugs used in case of liver diseases, lipotropic agents. ATC Code A05B.

Pharmacological properties.
Pharmacodynamics.
A small amount of ursodeoxycholic acid (UDCA) is usually found in human bile.
After oral administration it reduces bile cholesterol saturation, inhibiting its absorption in the small intestine and reducing cholesterol secretion into bile. Gradual dissolution of gallstones results from dispersion of cholesterol and formation of liquid crystals.
The effect of UDCA in hepatic and cholestatic diseases is thought to be due to a relative exchange of lipophilic, detergent-like, toxic bile acids for the hydrophilic, cytoprotective, non-toxic UDCA, as well as to an improvement in the secretory capacity of the hepatocytes and to immunoregulatory processes.
Use in children.
Cystic fibrosis.
There are data on prolonged use of UDCA (for the period of up to 10 years) during treatment of children with hepatobiliary disorders associated with cystic fibrosis. Particularly, the use of UDCA may reduce proliferation in the bile ducts, stop the development of histological changes and even remove hepatobiliary changes provided that therapy is started at the early stages of cystic fibrosis. For better effect, treatment with UDCA should be started immediately after cystic fibrosis is diagnosed.
Pharmacokinetics.
In oral administration, UDCA is rapidly absorbed in the small intestine and the upper part of ileum by passive transfer and in the terminal ileum by active transport. The absorption rate is usually 60-80%. After absorption, bile acid undergoes almost complete hepatic conjugation with amino acids glycine and taurine and is afterwards excreted with bile. Hepatic first-pass clearance is about 60%.
Depending on the daily dose and main disorder or condition of the liver, more hydrophilic UDCA is cumulated in the bile. At the same time, relative reduction in other more lipophilic bile acids is observed.
Under the influence of intestinal bacteria, a partial degradation to 7-ketolithocholic acid and lithocholic acid occurs. Lithocholic acid is hepatotoxic and causes damage to liver parenchyma in some animal

species. In humans, only its small fraction is absorbed, which is then sulfated in the liver and is thus detoxicated before being excreted with bile and, eventually, with feces.
The biological half-life period of UDCA is 3.5-5.8 days.

Clinical characteristics.

Indications.

Dissolution of radiolucent cholesterol gallstones with a diameter no more than 15 mm in patients with a functioning gallbladder, despite the presence of gallstone(s) in it.
Symptomatic treatment of primary biliary cirrhosis (PBC) in the absence of decompensated liver cirrhosis.
Treatment of bile reflux gastritis.
Treatment of hepatobiliary disorders in cystic fibrosis in children from 6 to 18 years of age.

Contraindications.

Hypersensitivity to any component of the drug.
Acute inflammation of the gallbladder or bile ducts.
Obturation of bile ducts (blockage of the common bile duct or gallbladder duct).
Frequent attacks of biliary (hepatic) colic.
The presence of radio-opaque calcified gallstones.
Impaired gallbladder contractility.
Decompensated liver cirrhosis.
Bad result of portoenterostomy or absence of adequate bile outflow in children with biliary tract atresia.

Interaction with other medicinal products and other kinds of interactions.

The drug Ukrliv® should not be co-administered with cholestyramine, colestipol or antacids that contain aluminum hydroxide and/or smectite, as these drugs bind UDCA in the intestine and thus prevent its absorption and reduce efficacy. If the use of the drug containing one of these substances is necessary, it should be taken not less than 2 hours before or 2 hours after the administration of the drug Ukrliv®.
UDCA may increase the absorption of cyclosporine in the intestine. Taking this into account, in patients taking cyclosporine, blood concentrations of this substance should be checked and the dosage adjusted, if necessary.
In isolated cases, UDCA may reduce the absorption of ciprofloxacin.
There are clinical data indicating that concomitant use of UDCA (500 mg/day) and rosuvastatin (20 mg/day) in healthy volunteers resulted in a slight increase of rosuvastatin plasma concentrations. The clinical significance of such interaction, as well as significance regarding other statins has not been defined.
It has been proved that UDCA reduces the peak plasma concentration (C_{max}) and the area under the curve (AUC) of the calcium antagonist nitrendipine in healthy volunteers. Close monitoring of the results of concomitant use of nitrendipine and UDCA is recommended. It may be necessary to increase the dose of nitrendipine.
Besides, reduction of the therapeutic effect of dapsone has been reported.
This information, as well as the data obtained *in vitro*, suggest that UDCA may potentially cause induction of cytochrome P450 3A enzymes. However, no such effect has been observed in a well-designed study of the interaction of UDCA with budesonide, which is a proven cytochrome P450 3A substrate.
Estrogenic hormones, as well as drugs that reduce blood cholesterol concentrations, such as clofibrate, may increase hepatic cholesterol secretion, and thus induce stone formation in the gallbladder, which is the opposite effect to UDCA used for dissolution of the stones.

Administration details.

The drug Ukrliv® should be used under medical supervision.
Within the first three months of treatment, the following liver function parameters should be checked: SGOT, SGPT and γ-GT every 4 weeks, and then – every 3 months. This also allows to detect the presence

or absence of response to treatment in patients with PBC, as well as detect potential liver dysfunctions, especially in patients with late-stage PBC, in a timely manner.
Use for dissolution of cholesterol gallstones.
In order to assess therapeutic progress and for timely detection of any signs of 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 (under ultrasound control) 6-10 months following the initiation of treatment.
The drug Ukrliv® should not be used if the gallbladder is not visualized on radiographs or in case of calcification of stones, gallbladder contractility disorder or frequent biliary colics.
Female patients taking Ukrliv® for dissolution of gallstones should use an effective non-hormonal method of contraception, since hormonal contraceptives may increase biliary lithiasis.
Treatment of patients with late-stage PBC.
In very rare cases, decompensation of liver cirrhosis has been observed, which partially regressed after the treatment was discontinued.
Patients with PBC may very rarely experience worsening of symptoms at the beginning of treatment, for instance, itching may increase. In such cases the dose of the drug Ukrliv® should be reduced to one tablet of Ukrliv® 250 mg per day; the dose should then be gradually increased, as described in section "Dosage and administration".
In case of diarrhea, it is recommended to reduce the dose of the drug, and in case of persistent diarrhea the treatment should be discontinued.
This pharmaceutical product contains less than 1 mmol (23 mg)/dose of sodium, therefore is practically sodium-free.

Use during pregnancy and breastfeeding.
Pregnancy
Animal studies have shown no effect of UDCA on fertility. The data on effect on fertility in humans are absent.
The data on the use of UDCA in pregnant women are insufficient. The results of animal studies reveal reproductive toxicity at the early stages of pregnancy. The drug Ukrliv® should not be used during pregnancy, unless it is absolutely necessary. Women of childbearing potential may take the drug only under the condition of using reliable contraception.
Women of reproductive age
It is recommended to use non-hormonal contraception or oral contraceptives with low estrogen content. Female patients using medicinal product Ukrliv® for dissolution of gallstones should use effective non-hormonal contraception, since hormonal oral contraceptives may increase the formation of stones in the gallbladder. The possibility of a pregnancy must be excluded before the initiation of treatment.
Breastfeeding.
According to several documented cases of using the drug in breastfeeding women, UDCA levels in breastmilk were very low, therefore no adverse reactions are to be expected in children receiving such milk.

Effect on reaction rate when driving motor transport or using other mechanisms.
No effect on the ability to drive motor transport and use other mechanisms has been observed.

Dosage and administration.
For patients with a body weight less than 47 kg or those having difficulty in swallowing tablets of the drug Ukrliv®, another dosage form is available - Ukrliv®, oral suspension.
For dissolution of cholesterol gallstones.
Approximately 10 mg of UDCA per kg of body weight per day (see table 1).

Table 1

Body weight (kg)	Number of tablets
up to 60	2
61-80	3
81-100	4
over 100	5

Tablets should be swallowed whole, without chewing, with water, once a day in the evening at bedtime.
Tablets should be taken on a regular basis.
The time required for dissolution of gallstones is generally in the range of 6-24 months. Treatment should be discontinued if gallstones do not decrease in size after 12 months of administration.
Therapeutic progress should be assessed every 6 months with the help of ultrasound or X-ray examination. Additional examinations should be used to check for calcified gallstones. If they are present, treatment should be discontinued.
For symptomatic treatment of primary biliary cirrhosis (PBC).
The daily dose depends on body weight and ranges from 3 to 7 tablets (14±2 mg of UDCA/kg of body weight).
During the first 3 months of treatment, the drug Ukrliv® should be taken during the day dividing the daily dose into several doses. When the indices of hepatic function improve, the daily dose may be administered once a day in the evening.

Table 2

Body weight (кг)	Daily dose (mg/kg b.w.)	Ukrliv®, 250 mg tablets			
		first 3 months			further
		morning	day	evening	evening (1 time a day)
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

Tablets should be swallowed without chewing, with water. The drug should be taken on a regular basis.
The use of the drug Ukrliv® in PBC may be continued indefinitely.
In patients with PBC, clinical symptoms may worsen in rare cases at the start of treatment, e.g. itching may increase. In this case, the therapy should be continued taking 1 tablet of Ukrliv® 250 mg per day, then the dose should be gradually increased (the daily dose is increased by 1 tablet each week) until the indicated dosage regimen is reached.
For treatment of bile reflux gastritis
250 mg of UDCA (1 tablet) once daily, with an adequate amount of water in the evening at bedtime.
For the treatment of bile reflux gastritis 250 mg UDCA should normally be taken for 10–14 days. The duration of treatment depends on the patient's condition. The physician should decide on the duration of treatment in each individual case.
Use in children.
In children with cystic fibrosis aged 6 years to 18 years the dosage is 20 mg/kg/day and is divided into 2-3 doses with further increase of the dose to 30 mg/kg/day if necessary.

Table 3

Body weight (kg)	Daily dose (mg/kg)	Ukrliv®, 250 mg tablets		
		Morning	Day	Evening
20–29	17-25	1	-	1
30–39	19-25	1	1	1
40–49	20-25	1	1	2
50–59	21-25	1	2	2
60–69	22-25	2	2	2
70–79	22-25	2	2	3
80–89	22-25	2	3	3
90–99	23-25	3	3	3
100–109	23-25	3	3	4
>110		3	4	4

Children.
For dissolution of cholesterol gallstones and symptomatic treatment of PBC
There are no principal age restrictions for the use of the drug Ukrliv® in children, however, children with a bodyweight below 47 kg and/or children having difficulty swallowing are recommended to use the drug in the form of suspension.
For the treatment of hepatobiliary disorders in cystic fibrosis
Use in children aged 6 years to 18 years.

Overdose.
In case of overdose diarrhea may occur. Other symptoms of overdose are unlikely because absorption of UDCA decreases with increasing dose and, therefore, a major part of the ingested dose is excreted with feces.
If diarrhea occurs, the dosage should be reduced, and treatment should be discontinued if diarrhea persists.
No specific measures are needed. The consequences of diarrhea should be treated symptomatically with restoration of fluid and electrolyte balance.
Additional information regarding special patient groups.
Long-term, high-dose UDCA therapy (28-30 mg/kg/day) in patients with primary sclerosing cholangitis (off-label use) was associated with a higher frequency of serious adverse events.

Adverse reactions.
Adverse reactions by organ systems and frequency are listed below: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10000, <1/1000), very rare (<1/10000, including isolated cases), unknown (frequency cannot be estimated from the available data).
Gastrointestinal tract: common – pasty stools, diarrhea; very rare - pronounced upper right abdominal pain.
Liver and gallbladder: very rare - calcification of gallstones, decompensation of liver cirrhosis which partially improved after treatment discontinuation.
Immune system: very rare - hypersensitivity reactions including rash (urticaria).
Reporting of suspected adverse reactions.
Reporting suspected adverse reactions after authorization 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 to the State Enterprise "State Expert Center of MOH of Ukraine" and to the applicant via the feedback form at the website: https://kusum.ua/pharmacovigilance/.

Shelf-life.
3 years.

Storage conditions.
Store at a temperature below 25 °C in the original package.
Keep out of reach of children.

Package.
10 tablets are in a blister; 3 or 10 blisters are in a carton package.

Conditions of supply.
By prescription.

Manufacturer.
LLC “KUSUM PHARM”.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy Oblast, Sumy, Skryabina Str., 54.

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