APPROVED
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INSTRUCTION
for medical use

UKRLIV®

Composition:
active substance: ursodeoxycholic acid;
1 tablet contains 500 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 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 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 visualised (oral cholecystography) with overview and occlusion views in standing and supine positions (under ultrasound control) 6-10 months following the beginning 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 stopped.
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 early stages of pregnancy. Pharmaceutical product, Ukrliv®, should not be used during pregnancy, except cases when it is essential Women of reproductive age may take the drug only on condition of using reliable contraception.
Women of reproductive age
It is recommended to use non-hormonal contraception or oral contraceptives with low estrogen content. Patients using the pharmaceutical product Ukrliv® for dissolving gall stones should use an effective non-hormonal contraception, since hormonal oral contraceptives may increase formation of stones in the gallbladder. The possibility of a pregnancy must be excluded before beginning 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 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/kg of body weight per day (see tab.1)

Table 1

Body weight (kg)	Number of tablets
to 60	1
From 61 to 80	1 ½ *
From 81 to 100	2
Over 100	2 ½ *

* 1 tablet of the drug Ukrliv®, 250 mg may be administered instead of ½ tablet of the drug Ukrliv® 500 mg.

Tablets should be swallowed whole, without chewing, with water, once a day in the evening before going to bed.
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 is approximately from 1 ½ to 3 ½ * tablets (14 ± 2 mg of UDCA/kg of bodyweight).
During the first 3 months of treatment, the pharmaceutical product 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 taken 1 time per day in the evening.

Table 2

Body weight (kg)	Daily dose (mg/kg of b.w.)	Ukrliv ®, tablets, 500 mg			
		first 3 months			further
		morning	day	evening	evening (1 time a day)
47-62	12–16	½ *	½ *	½ *	1 ½ *
63-78	13–16	½ *	½ *	1	2
79-93	13–16	½ *	1	1	2 ½ *
94-109	14–16	1	1	1	3
over 110		1	1	1 ½ *	3 ½ *

*Instead of ½ tablet of the pharmaceutical product Ukrliv®, 500 mg, one may take 1 tablet of the pharmaceutical product Ukrliv ®, 250 mg.

Tablets should be swallowed without chewing, followed with water. The drug should be taken regularly.
The use of the pharmaceutical product Ukrliv® in PBC may be unlimited in time.
In patients with PBC, the 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 one tablet of Ukrliv 250 mg per day, then the dose is gradually increased (daily dose is increased to reach the indicated dosage regimen every week).

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®, 500 mg tablets		
		Morning	Day	Evening
20–29	17-25	½ *	-	½ *
30–39	19-25	½ *	½ *	½ *
40–49	20-25	½ *	½ *	1
50–59	21-25	½ *	1	1
60–69	22-25	1	1	1
70–79	22-25	1	1	1 ½ *
80–89	22-25	1	1 ½ *	1 ½ *
90–99	23-25	1 ½ *	1 ½ *	1 ½ *
100–109	23-25	1 ½ *	1 ½ *	2
>110		1 ½ *	2	2

*Instead of ½ tablet of the pharmaceutical product Ukrliv®, 500 mg, one may take 1 tablet of the pharmaceutical product Ukrliv ®, 250 mg.

Children.
For dissolution of cholesterol gallstones and symptomatic treatment of PBC
There are no principal age restrictions for use of Ukrliv® in children, but children with bodyweight below 47 kg and/or children having difficulties with 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 diarrhoea may occur. Other symptoms of overdose are unlikely because absorption of UDCA decreases with increasing dose and therefore major part of the ingested dose is excreted in the feces.
If diarrhoea occurs, the dosage should be reduced, and treatment should be discontinued in case of persistent diarrhoea.
No specific measures are needed. The consequences of diarrhoea should be treated symptomatically with restoration of fluid and electrolyte balance.
Additional information regarding special populations.
Long-term, high-dose UDCA therapy (28-30 mg/kg/day) by 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), uncommon (frequency cannot be estimated from the available data).
Gastrointestinal disorders: common – pasty feces, diarrhea; very rare – pronounced upper right abdominal pain.
Liver and gallbladder: very rare - calcification of gallstones, decompensation of liver cirrhosis is observed which partially improved after treatment discontinuation.
Immune system disorders: very rare - Hypersensitivity 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 the 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.

Condition of supply.
By prescription.

Manufacturer.
LLC “KUSUM PHARM”.

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

or

Manufacturer.
KUSUM HEALTHCARE PVT LTD.

Address of manufacturer and manufacturing site.
Plot No. M-3, Indore Special Economic Zone, Phase-II, Pithampur, Distt. Dhar, Madhya Pradesh, Pin 454774, India.

or

Manufacturer.
LLC “GLADPHARM LLC”.

Address of manufacturer and manufacturing site.
40020, Ukraine, Sumy region, Sumy, Davydovskoho Hryhoriia Str., 54.

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