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INSTRUCTION
for medical use

UKRLIV®

Composition:
active substance: ursodeoxycholic acid;
5 ml of suspension contain 250 mg of ursodeoxycholic acid;
excipients: microcrystalline cellulose - sodium carboxymethylcellulose, benzoic acid (E 210), xylitol, glycerol, sodium saccharin, sodium chloride, citric acid, monohydrate; sodium citrate, lemon flavor, purified water.

Pharmaceutical form. Oral suspension.
Main physical and chemical properties: white viscous suspension with lemon flavor.

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.

Symptomatic treatment of primary biliary cirrhosis (PBC) in the absence of decompensated liver cirrhosis.
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.
Treatment of hepatobiliary disorders in cystic fibrosis in children aged from 1 month to 18 years.

Contraindications.

Hypersensitivity to bile acids or to any of the excipients of the drug.
Acute cholecystitis or acute cholangitis.
Bile ducts obturation (blockage of the common gallbladder duct or cystic duct).
Frequent episodes of biliary (hepatic) colic.
The presence of radio-opaque calcified gallstones.
Impaired gall bladder contractility.
Bad result of protoenterostomy or absence of adequate bile outflow in children with biliary tract atresia.

Interaction with other medicinal products and other kinds of interactions.

Medicinal product Укрлив® Ukrliv® should not be used concurrently with colestyramine, colestipol, or antacids, that contain aluminium hydroxide and/or smectite (aluminium oxide), 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 of 2 hours after the intake of the of the drug Ukrliv®.
UDCA may affect the absorption of cyclosporine from the intestine. Taking this into account, in patients treated with cyclosporine blood concentrations of this substance should be monitored and the dose should be 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 relevance of this interaction, also with 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.

Ukrliv® should be taken under medical supervision.
Within the first three months of treatment, the liver function parameters should be monitored every 4 weeks: AST (aspartate aminotransferase), ALT (alanine aminotransferease) and γ-GT (γ-glutamyl transferase).

Thereafter, these parameters are monitored every 3 months. This also permits to detect the presence or absence of response to treatment in patients with PBC, as well as timely detect potential liver dysfunctions, especially in patients with PBC at the late stages.

Use for dissolution of cholesterol gallstones.

To assess therapeutic progress and to timely identify any signs of calcification of the gallstones, depending on the size of the stones, 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.

Women taking the medicinal product 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 medicinal product Ukrliv® should be reduced to 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.

One measuring spoon (equivalent to 5 ml) of the medicinal product Ukrliv®, oral suspension, 250 mg/5 ml contains 0.34 mmol (7.95 mg) of sodium. Patients who control sodium intake (low sodium diet) should consider this fact.

Medicinal product Ukrliv®, oral suspension, 250 mg/5 ml contains xylitol: 1 ml of suspension contains 0.35 g of xylitol. Energy value of 1 g of xylitol is 2.4 kcal. A single dose of xylitol will be from 0.44 g (1.25 ml of suspension) to 12.25 g (35 ml of suspension) when taken as per recommended dose. When used a single dose of xylitol more than 10 g (more than 28.57 ml of suspension), it may have a laxative effect.

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. Medicinal product 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.

The following daily doses are recommended for various indications.

For dissolution of cholesterol gallstones

Approximately 10 mg of UDCA/kg of body weight per day (see tab.1).

Table 1

Body weight	Measuring spoon*	Equivalent in ml
From 5 to 7 kg	¼	1,25
From 8 to 12 kg	½	2,50
From 13 to 18 kg	¾ (= ¼ + ½)	3,75
From 19 to 25 kg	1	5,00
From 26 to 35 kg	1 ½	7,50
From 36 to 50 kg	2	10,00
From 51 to 65 kg	2 ½	12,50
From 66 to 80 kg	3	15,00
From 81 to 100 kg	4	20,00
Over 100 kg	5	25,00

* 1 measuring spoon (= 5 ml of suspension) contains 250 mg of UDCA.

Medicinal product Ukrliv® should be taken in the evening at bedtime. Suspension 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 identify 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 14 ± 2 mg of UDCA/kg of body weight).
During the first 3 months of treatment medicinal 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 administered once a day in the evening.

Table 2

Body weight (кг)	Daily dose (mg/kg b.w.)	Distribution of drug intake (measuring spoon * of Ukrliv® suspension)			
		first 3 months			*further*
		morning	day	evening	evening (1 time a day)
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	14-16	2	2	2	6
Over 115		2	2	3	7

* 1 measuring spoon (= 5 ml of suspension) contains 250 mg of UDCA.

To measure doses, a plastic disposable syringe without a needle can be used.
Medicinal product Ukrliv® should be taken according to the dosage regimen illustrated in tab. 2.
It is necessary to comply with the regular dosage regimen.
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, for instance, itching. If this happened, the therapy should be continued, first taking a reduced daily dose of Ukrliv®

suspension, thereafter the dose should be gradually increased (by increasing the daily dose every week) until the indicated dosage regimen is reached.

For treatment of hepatobiliary disorders in cystic fibrosis

For children with cystic fibrosis aged from 1 month 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.

Children with body weight less than 10 kg are affected very rarely. In such cases, for administration of the oral suspension, it is recommended to use single-use syringes which are commercially available.

Single doses for children with body weight up to 10 kg should be taken with a syringe from the measuring spoon that comes with the set, up to the volume of 1.25 ml. For this purpose a 2 ml single-use syringe with a 0.1 ml scale should be used.

Note that single-use syringes are not included in the package.

To administer the necessary dose with the syringe

1. Shake the suspension before opening the bottle/jar.
2. Pour a small amount of suspension to the measuring spoon.
3. Draw up into the syringe a little bit more suspension than required.
4. Press the plunger of the syringe with a finger to remove the air bubbles from the suspension.
5. Check the volume of suspension in the syringe, if necessary, adjust.
6. Do not draw the suspension into the syringe directly from the bottle/jar. Do not pour unused suspension from the measuring spoon or a syringe back into the bottle/jar.

Table 3

Dosage regimen for children with body weight less than 10 kg: 20 mg of UDCA*/kg/day (a single-use syringe is a volume measuring device)*

Body weight (kg)	Distribution of drug intake (ml of Ukrliv® suspension)	
	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

Table 4

Dosage regimen for children with body weight more than 10 kg: 20-25 mg of UDCA*/kg/day (a measuring spoon is a volume measuring device)*

Body weight (kg)	Daily dose of UDCA (mg/kg of body weight)	Distribution of drug intake (a measuring spoon* of Ukrliv® 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	1¼
27-29	22-23	1¼	1¼
30-32	21-23	1¼	1½
33-35	21-23	1½	1½
36-38	21-23	1½	1¾
39-41	21-22	1¾	1¾
42-47	20-22	1¾	2
48-56	20-23	2¼	2¼
57-68	20-24	2¾	2¾
69-81	20-24	3¼	3¼
82-100	20-24	4	4
>100		4½	4½

Table 5

* Comparison table

	Oral suspension	UDCA
1 measuring spoon	= 5 ml	= 250 mg
¾ measuring spoon	= 3,75 ml	= 187,5 mg
½ measuring spoon	= 2,5 ml	= 125 mg
¼ measuring spoon	= 1,25 ml	= 62,5 mg

Children.
For dissolution of cholesterol gallstones and symptomatic treatment of PBC
There are no age restrictions for the use of this medicinal product. Dosage according to the section "Dosage and administration".
For treatment of hepatobiliary disorders in cystic fibrosis
Use in children aged from 1 month.

Overdose.
In the case of overdose diarrhea may occur. Overdose is unlikely, since absorption of UDCA is reduced when increasing the dose and therefore most of the dose taken is excreted in feces.
If diarrhea occurs, dosage should be reduced, and if diarrhea persists, therapy should be discontinued.
No specific measures are to be taken; 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.
After the first opening of the jar or bottle, store not more than 4 months.

Package.
30 ml or 200 ml of suspension are in a bottle; or 40 ml in a jar. Each bottle or jar is in a carton package together with a measuring spoon.

Conditions of supply.
By prescription.

Manufacturer.
LLC "KUSUM PHARM".

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

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