CONTRAINDICATIONS (URSO is contraindicated in the following patients.)
(1) Patients with complete biliary obstruction [Symptoms may be aggravated due to choleretic action.]
(2) Patients with fulminant hepatitis [Symptoms may be aggravated.]

DESCRIPTION
<table>
<thead>
<tr>
<th>Tablets 50 mg</th>
<th>Tablets 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active ingredient (per tablet)</td>
<td>Ursodeoxycholic acid (JP) 50 mg</td>
</tr>
<tr>
<td>Inactive ingredient</td>
<td>Hydroxypropylcellulose, magnesium stearate, cellulose, corn starch, carmellose calcium, light anhydrous silicic acid</td>
</tr>
</tbody>
</table>

Description/dosage form
- White/ odorless/ bitter taste/ plain tablet
- White/ odorless/ bitter taste/ plain tablet (scored)

Appearance
- Tablets 50 mg: Diameter (mm) 6.0, Thickness (mm) ca. 2.4, Weight (mg) 75
- Tablets 100 mg: Diameter (mm) 8.0, Thickness (mm) ca. 2.7, Weight (mg) 150

Identification code
- Tablets 50 mg: 234
- Tablets 100 mg: 235

INDICATIONS/ DOSAGE AND ADMINISTRATION
- Choleretic effect in the following diseases: disease of biliary system including biliary tract and gallbladder, and cholestatic liver disease
- Improvement of liver function in chronic liver disease
- The usual adult dosage for oral use is 50 mg of ursodeoxycholic acid (UDCA) 3 times daily. The dosage may be adjusted according to the patient's age and symptoms.

- Dyspepsia in the following diseases: sequelae of small intestine resection and inflammatory disease of small intestine
- Dissolution of cholesterol gallstones without shell calcification
  For dissolution of cholesterol gallstones without shell calcification, the usual adult dosage for oral use is 600 mg of ursodeoxycholic acid daily in 3 divided doses. The dosage may be adjusted according to the patient's age and symptoms.

- Improvement of liver function in primary biliary cirrhosis
  For improvement of liver function in primary biliary cirrhosis, the usual adult dosage for oral use is 600 mg of ursodeoxycholic acid daily in 3 divided doses. The dosage may be adjusted according to the patient's age and symptoms. The maximum daily dosage should be within 900 mg.

- Improvement of liver function in chronic liver disease due to hepatitis C virus
  For improvement of liver function in chronic liver disease due to hepatitis C virus, the usual adult dosage for oral use is 600 mg of ursodeoxycholic acid daily in 3 divided doses. The dosage may be adjusted according to the patient's age and symptoms. The maximum daily dosage should be within 900 mg.
Improvement of liver function in primary biliary cirrhosis:
- URSO should be carefully administered to patients with biliary cirrhosis accompanied by severe jaundice since their symptoms may be aggravated. Appropriate therapeutic measures such as discontinuing this product should be taken, if any abnormalities including increased serum bilirubin are observed.

Improvement of liver function in chronic liver disease due to hepatitis C virus:
- In patients with chronic liver disease due to hepatitis C virus, it is recommended to primarily perform virus elimination therapy prior to using this product. It should be considered to administer this product to the patients who have not responded to virus eliminating therapy with interferon or those who are inapplicable to interferon therapy, since this product has no antiviral activity and it has not been well established whether the improvement of liver function has good influence on the long-term prognosis of chronic liver disease due to hepatitis C virus.
- In patients with decompensated cirrhosis, the efficacy and safety of this product have not been established. This product should be carefully administered to patients with severe jaundice since symptoms may be aggravated. Appropriate therapeutic measures such as discontinuing this product should be taken, if any abnormalities including increased serum bilirubin are observed.

### PRECAUTIONS

1. **Careful Administration (URSO should be administered with care in the following patients.)**
   - (1) Patients with severe pancreatic diseases [Pancreatic diseases may be aggravated.]
   - (2) Patients with peptic ulcers [Symptoms may be aggravated due to mucosal irritant action of this product.]
   - (3) Patients with gallstones in biliary tract [Cholestasis may be induced due to choleretic action of this product.]

2. **Drug Interactions**

   **Precautions for coadministration (URSO should be administered with care when coadministered with the following drugs.)**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Signs, Symptoms, and Treatment</th>
<th>Mechanism and Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral sulfonylurea hypoglycemic agents (tolbutamide, etc.)</td>
<td>Hypoglycemic action may be intensified. This product is reported to inhibit binding of tolbutamide to serum albumin.</td>
<td></td>
</tr>
<tr>
<td>Colestyramine, etc.</td>
<td>Intervals of administration should be increased if possible, since the effects of this product may be reduced.</td>
<td>These drugs may delay or decrease the absorption of this product since they bind it.</td>
</tr>
</tbody>
</table>

### 3. Adverse Reactions

#### Indications except improvement of liver function in primary biliary cirrhosis and in chronic liver disease due to hepatitis C virus

Two hundred and twenty-two (222) adverse reactions were reported in 182 patients (3.13%) of total 5,807 patients. Main adverse reactions were 6 events of diarrhea (1.91%), 16 events of nausea (0.28%), 10 events of itching (0.17%), 8 events of increased AST (GOT) (0.14%) and 8 events of increased ALT (GPT) (0.14%). (Data available at the time of notification of reevaluation results in 1996, including those of URSO granules 5%)

#### Improvement of liver function in primary biliary cirrhosis

**<Clinical studies for NDA>**

Twelve (12) adverse reactions were reported in 10 patients (10.87%) of total 92 patients. Main adverse reactions were 2 events of diarrhea (2.17%), 2 events of itching (2.17%) and 2 events of rash (2.17%). (Data available at the time of approval of the additional indication)

**<Special survey in patients using the drug for long periods>**

Two hundred and fifty-three (253) adverse reactions were reported in 184 patients (10.12%) of total 1,462 patients. Based on calculation by duration of administration, 125 adverse reactions were reported in 84 patients (5.75%) of total 1,461 patients treated with this product for less than 1 year, 54 adverse reactions in 42 patients (3.26%) of total 1,287 patients for 1 to less than 2 years, 28 adverse reactions in 21 patients (1.79%) of total 1,171 patients for 2 to less than 3 years, 24 adverse reactions in 18 patients (1.80%) of total 998 patients for 3 to less than 4 years, and 22 adverse reactions in 18 patients (2.28%) of total 789 patients for 4 years or over. Main adverse reactions were 11 events of diarrhea and 10 events of itching. (Data available at the end of reexamination period)

#### Improvement of liver function in chronic liver disease due to hepatitis C virus

**<Clinical studies for NDA>**

Two hundred and thirty-three (233) adverse reactions were reported in 144 patients (24.16%) of total 596 patients. Main adverse reactions were 41 events of diarrhea (6.88%), 21 events of loose stools (3.52%), 15 events of constipation (2.52%) and 12 events of itching (2.01%). (Data available at the time of approval of the additional indication)
<Post-marketing surveillance for the safety and efficacy in the actual usage of this product in patients with chronic liver disease due to hepatitis C virus>

Fifty-four (54) adverse reactions were reported in 47 patients (2.44%) of total 1,923 patients. Main adverse reactions were 9 events of diarrhea (0.47%), 5 events of constipation (0.26%), 4 events of abdominal distension (0.21%), 4 events of gastric discomfort (0.21%) and 3 events of itching (0.16%).

(1) Clinically significant adverse reactions

Interstitial pneumonia (incidence unknown): Interstitial pneumonia with fever, cough, dyspnea and X-ray abnormalities may occur. If any signs of interstitial pneumonia are observed, administration should be discontinued and appropriate therapeutic measures, including the administration of adrenocorticotropic hormone, should be taken.

<table>
<thead>
<tr>
<th>Incidence Type</th>
<th>Incidence</th>
<th>5% ≥ 1%</th>
<th>1% ≥ 0.1%</th>
<th>&lt;0.1%</th>
<th>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea</td>
<td>Nausea, anorexia, constipation, heartburn, gastric discomfort, abdominal pain, abdominal distension</td>
<td>Vomiting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>Itching, rash</td>
<td>Urticaria, etc.</td>
<td>Erythema (multiforme exudativum etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>Increased AST (GOT), increased ALT (GPT), increased ALP</td>
<td>Increased bilirubin, increased yGTP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>Malaise, dizziness</td>
<td>Decreased white blood cell count</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The incidences of adverse reactions listed in the table were calculated based on the results of reevaluation, clinical studies for NDA, and post-marketing survey.

Note) In the event of such symptoms, appropriate measures such as discontinuation of administration, should be taken.

4. Use in the Elderly

Dosage adjustment or other appropriate measures should be considered when prescribing URSO, since elderly patients often have reduced physiological function.

5. Use during Pregnancy, Delivery or Lactation

URSO is not recommended to be administered to pregnant women or women who may possibly be pregnant. Animal studies in rats have shown embryo/fetal toxicity, i.e. fetal resorption, when administering at the excessive daily dose of 2,000 mg/kg before pregnancy and during early stage of pregnancy.

6. Precautions concerning Use

<Precautions regarding dispensing>

For drugs that are dispensed in a press-through package (PTP), instruct the patient to remove the drug from the PTP sheet prior to use. [It was reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.]

PHARMACOKINETICS

1. Serum concentrations

Peak serum UDCA concentrations after administration of 200 mg of UDCA (two 100 mg tablets) and 400 mg (four 100 mg tablets) to 6 healthy adults were 1.90±0.25 μg/mL and 7.09±1.43 μg/mL, respectively.

2. Absorption and excretion

Major serum metabolites after administration of 400 mg of UDCA (four 100 mg tablets) to 6 healthy adults were glyco- and cholic acid (GUDCA) and its sulfate conjugate (GUDCA-S). Major urinary metabolites were GUDCA-S and N-acetylglucosamine conjugate of UDCA, and 0.25% and 0.11%, respectively, of the dose were excreted into urine up to 24 hours after administration.

3. Absorption and metabolism (foreign data)

14C-UDCA was intravenously administered to healthy volunteers (Americans) after repeated oral administration at a dose of 1 g/day of UDCA for 2 weeks. The absorbed amount was determined using the isotope dilution method. The UDCA pool size in the enterohepatic circulation was about 940 mg, and almost the entire UDCA administered entered the enterohepatic circulation. In addition, UDCA accounted for up to 56% of the bile acid fraction in the bile. The percentages of both chenodeoxycholic acid (CDCA) and cholic acid (CA) to the bile acid fraction decreased. (N.B.: The approved daily dosages of URSO are different from dosages used in the pharmacokinetic studies.) [See “DOSAGE AND ADMINISTRATION” section]

CLINICAL STUDIES

<Double-blind clinical trials>

1. UDCA (150 mg/day) was administered orally for 2 weeks to patients with diseases of the biliary tract (cholelithiasis, cholecystitis, biliary dyskinesia and post-cholecystectomy syndrome) in order to evaluate its efficacy on subjective symptoms. Symptoms such as right hypochondrial pain improved significantly compared to the placebo control group. 3)

2. UDCA (150 mg/day) was administered orally for 4 weeks to patients with chronic liver diseases (chronic hepatitis and liver cirrhosis). AST (GOT) and ALT (GPT) levels decreased significantly in the UDCA group compared to the placebo group. 4)
3. UDCA (150 and 600 mg/day) was administered orally to patients with cholesterol gallstones for 6 to 12 months in order to evaluate its cholelitholytic activity. UDCA was effective (stones disappeared or their size or number decreased as judged based on X-ray films) in 4/23 patients (17.4%) in the 150 mg/day group and 10/29 patients (34.5%) in the 600 mg/day group, compared to 1/20 patients (5.0%) in the placebo group. Litholytic activity was significant in the 600 mg/day group compared to the placebo group.3)

4. UDCA (150 and 600 mg/day) was administered orally to patients with primary biliary cirrhosis (PBC) for 24 weeks in order to evaluate its effects on liver functions. Marked improvement or improvement was seen in 5/22 patients (22.7%) in the 150 mg/day group and 23/25 patients (92.0%) in the 600 mg/day group. Improvement was significant in the 600 mg/day group compared to the 150 mg/day group.5)

5. UDCA (150, 600, and 900 mg/day) was administered orally to patients with chronic liver disease due to hepatitis C virus for 24 weeks in order to evaluate the percentage change (median) of ALT (GPT) level. The percentage changes were -15.3% (195 patients) in the 150 mg/day group, -29.15% (198 patients) in the 600 mg/day group, and -36.2% (193 patients) in the 900 mg/day group. Decrease in ALT (GPT) level was significant in the 600 mg/day group and 900 mg/day group compared to the 150 mg/day group. The incidence of adverse reactions was similar with no significant difference among groups: 18.1% (36/199 patients), 21.5% (43/200 patients), and 17.8% (35/197 patients) in the 150 mg/day, 600 mg/day, and 900 mg/day groups, respectively. Diarrhea was observed more frequently in the higher dose group.7)

6. UDCA (600 mg/day) was administered orally to patients with primary biliary cirrhosis (PBC) for 48 to 132 weeks in order to evaluate its effects on liver functions. Marked improvement or improvement was seen in 27/33 patients (81.8%).9)

7. In the patients with chronic liver disease due to hepatitis C virus who were administered with UDCA at 600 mg/day (if necessary the dose was increased to 900 mg/day) for at least 1 year, the effect was confirmed to last as shown by the significant decrease of ALT (GPT) by -43.4% (median) in 257 patients.9)

PHARMACOLOGY

1. Cholestatic effect and improvement of cholestasis
   (1) UDCA (150 mg/day) was orally administered for 14 days to 5 patients with T-tube drainage after surgical removal of gallstones. UDCA increased hepatic bile flow from 5th day after the administration.10)
   (2) UDCA (24 or 35 mg/kg) was intraduodenally administered to rats with estradiol-17β-D-glucuronide-induced acute intrahepatic cholestasis. UDCA suppressed the decrease in bile flow.11)
   (3) UDCA (20 or 60 mg/kg/day) was administered for 7 days to rats with 17α-ethinyl estradiol-induced chronic intrahepatic cholestasis. UDCA suppressed the decrease in bile flow.11)

2. Improvement of liver function
   (1) Improvement of liver uptake-excretion function12)
     Kinetic analysis was conducted by i.v. injection of 99mTc-PMT in chronic liver disease patients before and after oral administration of UDCA (150 mg/day) for 3 months. The liver uptake-excretion curve peak time shortened significantly.
   (2) Inhibition of liver injury in animal models
      1) Autoimmune hepatitis model mice were fed with feed containing 0.3% UDCA. Mortality of the mice by injection of lipopolysaccharide was decreased. Increase of blood AST (GOT) and ALT (GPT) levels, necrosis of hepatic tissues, and inflammatory cell infiltration were also prevented.13)
      2) In concanavalin A-induced liver injury mice orally administered UDCA (50 and 150 mg/kg), UDCA suppressed the increase in blood AST (GOT) and ALT (GPT) levels.14) In the same mice orally administered UDCA (150 mg/kg), UDCA also suppressed the increase in blood TNF-α, IL-6, and MIP-2 (equivalent to human IL-8).15) Moreover, UDCA suppressed the increase in myeloperoxidase (MPO) as an indicator of the infiltration of neutrophiles into the liver.14)
      3) In chenodeoxycholic acid (CDCA)-induced liver injury hamsters orally administered UDCA (50 and 150 mg/kg), UDCA suppressed the increase in blood ALT (GPT) level.15)
   (3) Alleviation of hydrophobic bile acid-induced hepatotoxicity16)
      CA, CDCA or UDCA was added to human hepatocyte-derived Chang cells in order to evaluate their cytotoxicity. CDCA was most cytotoxic, and cytotoxicity of UDCA or CA was weak and was comparable. The cytotoxicity of CDCA was decreased significantly upon the simultaneous addition of UDCA.
   (4) Inhibition of cytokine/chemokine production (in vitro)
      UDCA suppressed the production of TNF-α and IL-6 in co-culturing with mouse liver nonparenchymal cells and lymph mode cells stimulated by concanavalin A.17) UDCA suppressed the production of RANTES in rat hepatocytes stimulated by TNF-α.18)

3. Improvement of digestion and absorption
   (1) UDCA (150 mg/day) was administered for 1 month to 12 patients who underwent ileotomy, and blood higher fatty acid and fat-soluble vitamin levels were determined before and after treatment. Blood linoleic acid, linolenic acid, vitamins D and E levels were increased.19)
   (2) Promotion of secretion of pancreatic juice20)
      UDCA (2.55x10^-2M) was administered into the duodenum of rats and dogs at 2.5 mL/kg. UDCA increased pancreatic juice volume in rats, while it increased pancreatic bicarbonate concentration and enzyme (amylase, etc.) activities in dogs.
4. Dissolution of gallstones

(1) Desaturation of cholesterol in gallbladder bile
UDCA was orally administered to 5 patients with cholesterol gallstones at 300 mg/day for 2 months and at 600 mg/day for an additional 2 months. The relative cholesterol content in gallbladder bile decreased at both doses, resulting in an improvement of the lithogenic index.

(2) Liquid crystal formation
UDCA (600 mg/day) was orally administered to 5 patients with cholesterol gallstones for 1 week. Gallbladder bile samples were examined under a polarizing microscope. Lyotropic liquid crystals were observed, and a large amount of cholesterol was solubilized in these liquid crystals.

(3) Inhibition of cholesterol absorption from the intestine
UDCA (600 mg/day) was orally administered to 6 healthy adults for 1 month. UDCA inhibited cholesterol absorption from the intestine.

5. Mechanisms of action
UDCA increases bile secretion (choleretic effect) and thereby improves cholestasis. When administered, UDCA replaces hydrophobic bile acids which show potent cytotoxicity in the liver and increases its relative ratio in total bile acids, resulting in alleviation of hydrophobic bile acid-induced hepatotoxicity (replacement). Moreover, UDCA inhibits cytokine/chemokine production and the infiltration of inflammatory cells into the liver, leading to improvement of liver dysfunction. In addition to these effects, UDCA, as mentioned above, is known to provide dissolution of gallstones and improvement of digestion and absorption.

PHYSICOCHEMISTRY
Nonproprietary name: Ursodeoxycholic Acid (JAN)
Chemical name: 3α,7β-Dihydroxy-5β-cholan-24-oic acid
Molecular formula: C24H40O4
Molecular weight: 392.57

Description:
UDCA occurs as white crystals or powder. It has a bitter taste. It is freely soluble in methanol, in ethanol (99.5) and in acetic acid (100), and practically insoluble in water.
Melting point: 200-204 °C

PACKAGING
URSO Tablets 50 mg:
Boxes of 100 (10 tablets x 10) and 1,000 (10 tablets x 100) in press-through packages
Bottles of 500

URSO Tablets 100 mg:
Boxes of 100 (10 tablets x 10), 1,000 (10 tablets x 100), 5,000 (10 tablets x 500) and 2,100 (21 tablets x 100) in press-through packages
Bottles of 500

REFERENCES
9) Mitsubishi Tanabe Pharma Corporation: The long-term clinical study of MT-711 (ursodeoxycholic acid) in patients with chronic liver disease due to hepatitis C (internal report)
11) Mitsubishi Tanabe Pharma Corporation: Report No.1 on the pharmacology of ursodeoxycholic acid (internal report)
17) Mitsubishi Tanabe Pharma Corporation: Report No.2 on the pharmacology of ursodeoxycholic acid (internal report)
18) Mitsubishi Tanabe Pharma Corporation: Report No.3 on the pharmacology of ursodeoxycholic acid (internal report)
20) Hara, Y. et al.: Fukuoka Acta Medica, 1974; 65(12):933-940

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