TOWA PHARMACEUTICAL CO., LTD.

※※ Revised: October 2016 (____ part: 8th version, description: identification code, appearance)
Revised: June 2013 (7th version, sales name change etc)

Improving agent for hepatic, biliary and digestive functions

Ursodeoxycholic Acid Tablets, Japanese Pharmacopoeia
URDESTON® TABLETS 100mg

Storage:
Store at room temperature.

Expiration date:
Indicated on the package and label.

Standard Commodity Classification No. of Japan 872362	
Approval No.	22500AMX00723
Date of listing in the NHI reimbursement price	June 2013
Date of initial marketing in Japan	July 1997
Date of addition of indication	January 2010
Date of reevaluation (quality)	September 2004

CONTRAINDICATIONS (URDESTON 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

Active ingredient per tablet	Ursodeoxycholic Acid (JP) ····· 100 mg		
Inactive ingredients	Corn Starch, Microcrystalline Cellulose, Povidone, Croscarmellose Sodium, Light Anhydrous Silicic Acid, Magnesium Stearate		
Product description	White uncoated tablets with a score on one side. They are odorless, and have a bitter taste.		
※※ Identification code	Tablet	Tw U02	
	Package	Tw. U02	
※※ Appearance	Top surface 	Bottom surface 	Side surface 
Diameter (mm)	8.0		
Thickness (mm)	2.7		
Weight (mg)	150		

INDICATIONS

1. · Choleretic effect in the following diseases
   Biliary disease (bile duct and gallbladder) and hepatic disease with cholestasis
   · Improvement of hepatic function in chronic hepatic disease
   · Dyspepsia in the following diseases
   Sequela of small intestinal resection and inflammatory small intestinal disease
2. Dissolution of cholesterol gallstones without shell calcification
3. Improvement of hepatic function in primary biliary cirrhosis
4. Improvement of hepatic function in chronic hepatic disease due to hepatitis C virus

PRECAUTIONS FOR INDICATIONS

Improvement of hepatic function in primary biliary cirrhosis:

· Since symptoms may be aggravated in patients in the stage of hepatization with severe jaundice, this product must be administered with care. When increase in serum bilirubin level, etc. is noted, appropriate measures such as discontinuation of this product should be taken.

Improvement of hepatic function in chronic hepatic disease due to hepatitis C virus:

· For chronic hepatic disease due to hepatitis C virus, eradication of virus is recommended at first. Since this product does not have an effect of virus eradication and effect of improvement of hepatic function on long-term prognosis of chronic hepatic disease due to hepatitis C virus is not clarified at this time, administration of this product should be considered in patients unresponsive to interferon therapy for eradication of virus or who are not applicable to interferon therapy.

· The efficacy and safety in patients with decompensated cirrhosis have not been established. Since symptoms may be aggravated in patients with severe jaundice, this product must be administered with care. When increase in serum bilirubin level, etc. is noted, appropriate measures such as discontinuation of this product should be taken.

DOSAGE AND ADMINISTRATION

1. The usual adult dosage for oral use is 50 mg of ursodeoxycholic acid 3 times daily. The dosage may be adjusted according to the patient's age and symptoms.
2. 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.
3. For improvement of hepatic 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. Dosage may be increased up to 900 mg per day.
   For improvement of hepatic function in chronic hepatic 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. Dosage may be increased up to 900 mg per day.

PRECAUTIONS

1. **Careful Administration** (URDESTON should be administered with care in the following patients.)
   1) Patients with serious pancreatic diseases [Pancreatic diseases may be aggravated.]
   2) Patients with peptic ulcer [Symptoms may be aggravated due to mucosal irritant action of this product.]
   3) Patients with gallstones in bile duct [Cholestasis may be induced due to choleretic action of this product.]

2. **Drug Interactions**

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

Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Oral sulfonylurea hypoglycemic agents Tolbutamide etc.	Hypoglycemic action may be intensified.	This product is reported to inhibit binding of tolbutamide to serum albumin.
Colestyramine etc.	Administration interval should be taken as much as possible, since the effects of this product may be reduced.	These drugs may bind with this product and delay or decrease its absorption.
Antacids Aluminum hydroxide gel etc.	The effects of this product may be reduced.	Antacids containing aluminum may absorb this product and interfere with its absorption.
Hypolipidemic agents Clofibrate etc.	The effects of this product may be reduced when used for dissolution of cholesterol gallstones.	Clofibrate may encourage cholesterol gallstone formation since it increases cholesterol secretion into bile.

3. **Adverse Reactions**

No investigation such as a drug use investigation clearly showing the incidence of adverse reactions has been conducted.

1) **Clinically significant adverse reactions (incidence unknown)**
   Interstitial pneumonia: Interstitial pneumonia accompanied with fever, cough, dyspnea, or abnormal chest X-ray findings may occur. If such symptoms occur, administration of this product should be discontinued and appropriate measures such as administration of adrenocortical hormone should be taken.
2) Other adverse reactions

	Incidence unknown
Gastrointestinal	Diarrhea, nausea, anorexia, constipation, heartburn, vomiting, stomach discomfort, abdominal pain, abdominal distension
Hypersensitivity	Pruritus, rash*, urticaria*, erythema (erythema multiforme exudativum etc.)*, etc.
Hepatic	Increased AST(GOT), increased ALT(GPT), increased Al-P, increased bilirubin, increased γ-GTP,
Others	General malaise, dizziness, leukocytopenia

*: If such symptoms occur, appropriate measures such as discontinuation of treatment should be taken.

4. **Use in the Elderly**

Since elderly patients often have reduced physiological functions, administration should be given with care to the dosage.

5. **Use during Pregnancy, Delivery or Lactation**

It is not recommended to administer this product to pregnant women or women who may possibly be pregnant. [Massive dose administration of this product (2000 mg/kg/day) in rats in the pre-pregnancy stage and the early stage of pregnancy showed fetal toxicity (fetal resorption).]

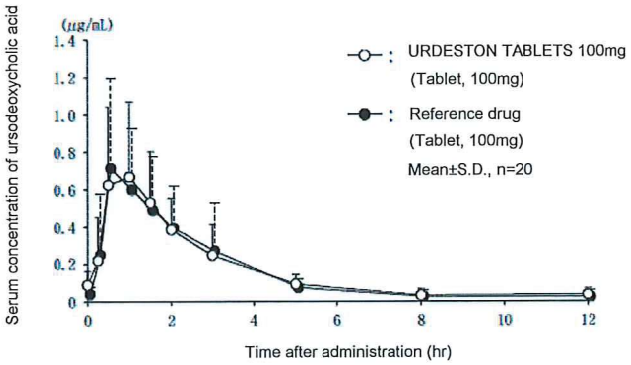
6. **Precautions Concerning Use**

Precautions regarding dispensing:
For drugs that are dispensed in a PTP (press-through package) sheet, instruct the patient to remove the drug from the package prior to use. [It has been 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

Bioequivalence test

One tablet each of URDESTON TABLETS 100mg and a reference drug (as 100 mg of ursodeoxycholic acid) was administered orally as a single dose to healthy adult men (n=20) under fasting conditions in a crossover design to measure each unchanged drug concentration in serum. Obtained pharmacokinetic parameters (AUC and Cmax) were statistically analyzed, demonstrating the bioequivalence of these drugs (based on PAB/PCD Notification No. 718, May 30, 1980)[1].



	Determined parameter		Reference parameter
	AUC_{12} (μg·hr/mL)	Cmax (μg/mL)	Tmax (hr)
URDESTON TABLETS 100mg (Tablet, 100 mg)	1.99±0.59	0.87±0.39	1.28±0.88
Reference drug (Tablet,100 mg)	1.91±0.58	0.92±0.38	1.23±0.91

(Mean±S.D., n=20)

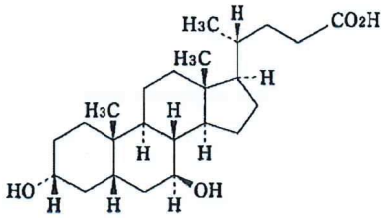
Serum concentration and parameters such as AUC and Cmax may differ according to study conditions such as selection of subjects and frequency/time of body fluid sample collection.

Dissolution profile

URDESTON TABLETS 100mg has been confirmed to conform to the dissolution standard of Ursodeoxycholic Acid Tablets defined in the official monographs of the Japanese Pharmacopoeia[2].

PHYSICOCHEMISTRY

Structural formula:



Nonproprietary name:
Ursodeoxycholic Acid
Chemical name:
3α,7β-Dihydroxy-5β-cholan-24-oic acid
Molecular formula:
$C_{24}H_{40}O_4$
Molecular weight:
392.57
Description:
Ursodeoxycholic Acid occurs as a white crystal or powder, with 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

PRECAUTIONS FOR HANDLING

Stability test
In an accelerated test using final packaged products (at 40°C and 75% relative humidity for 6 months), URDESTON TABLETS 100mg was estimated to be stable for 3 years under normal distribution conditions[3].

PACKAGING

URDESTON TABLETS 100mg:
Boxes of 100 tablets, 1,000 tablets in press-through packages
Polyethylene containers of 1,000 tablets

REFERENCES

1) Internal data of Towa Pharmaceutical Co., Ltd.: Bioequivalence test
2) Internal data of Towa Pharmaceutical Co., Ltd.: Dissolution test
3) Internal data of Towa Pharmaceutical Co., Ltd.: Stability test

CONTACT INFORMATION ON REQUEST FOR LITERATURE AND PRODUCT INFORMATION

Please request references (including internal data) to the following address.

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