PRODUCT MONOGRAPH

[Pr]Dom-URSODIOL C

Ursodiol Tablets USP

250 mg & 500 mg

Cholestatic Liver Diseases

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 250 mg, 500 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

Dom-URSODIOL C (ursodiol), also known as ursodeoxycholic acid (UDCA) is indicated for:

- the management of cholestatic liver diseases, such as primary biliary cirrhosis (PBC).

Cholestatic liver diseases are characterized by a decrease in bile secretion and bile flow.

The diagnosis of cholestatic liver diseases is based on the biochemical signs of cholestasis (such as an increase in alkaline phosphatase, γ-GT, bilirubin), and also an increase in IgM levels and the presence of antimitochondrial antibodies in PBC.

The monitoring of ursodiol in the management of cholestatic liver diseases should be based on the biochemical parameters of cholestasis, as described above, as well as on signs of hepatic cytolysis (such as AST, ALT) which are very often associated with cholestasis during the progression of the diseases.

Therefore, liver function tests (γ-GT, alkaline phosphatase, AST, ALT), and bilirubin level should be monitored every month for three months after start of therapy, and every six months thereafter. Serum levels of these parameters usually decrease rapidly. Improved serum liver tests (e.g. AST, ALT) do not always correlate with improved disease status. Treatment should be discontinued if the levels of the above parameters increase (see WARNINGS and PRECAUTIONS).

Dom-URSODIOL C is not indicated for the treatment of decompensated cirrhosis.

Geriatrics:
Appropriate studies with ursodiol have not been performed in the geriatric population. However, geriatric-specific problems that would limit the use or usefulness of ursodiol in the elderly are not expected.

Pediatrics:
The safety and effectiveness of ursodiol in children have not been established.

CONTRAINDICATIONS

Patients who are hypersensitive or intolerant to ursodiol or to any ingredient in the formulation. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

Carcinogenesis and Mutagenesis
Ursodiol has no carcinogenic, mutagenic or teratogenic effects in laboratory animals treated at higher doses than those intended for therapy in humans, and after long-term treatment (see TOXICOLOGY).

Hepatic/Biliary/Pancreatic
Patients with variceal bleeding, hepatic encephalopathy, ascites, or in need of an urgent liver transplant, should receive appropriate specific treatment.

Special Populations

Pregnant Women: There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Dom-URSODIOL C should not be used in women who are or may become pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the foetus. (See also TOXICOLOGY.)

Nursing Women: It is not known whether ursodiol is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when Dom-URSODIOL C is administered to a nursing mother.

Pediatrics: The safety and effectiveness of ursodiol in children has not been established.

Geriatrics: Appropriate studies with ursodiol have not been performed in the geriatric population. However, geriatric-specific problems that would limit the use or usefulness of ursodiol in the elderly are not expected.

Monitoring and Laboratory Tests

Lithocholic acid, one of the metabolites of ursodeoxycholic acid is hepatotoxic unless it is effectively detoxified in the liver. Therefore, the following tests are important for patient monitoring:

Liver function tests (γ-GT, alkaline phosphatase, AST, ALT), and bilirubin levels should be monitored every month for three months after start of therapy, and every six months thereafter. Serum levels of these parameters usually decrease rapidly. Improved serum liver tests (e.g. AST, ALT) do not always correlate with improved disease status. Treatment should be discontinued if the levels of the above parameters increase.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse events observed in clinical trials are tabulated and described below. In a 180 patient placebo-controlled trial in primary biliary cirrhosis, the common adverse events (i.e. ≥ 1 %) included leukopenia, skin rash, diarrhea, blood creatinine increased, blood glucose increased, and peptic ulcer. In a second trial with 60 patients, the frequency of treatment-emergent adverse event reporting was higher with the most common (defined as ≥ 5%) being asthenia, dyspepsia, edema peripheral, hypertension, nausea, GI disorder, chest pain, and pruritus. In this second trial there were 4 serious adverse events: 1 patient with diabetes mellitus, 1 patient with breast nodule and 2 patients with fibrocystic breast disease. None of these events were considered related to the medication. At the recommended dosage, ursodiol is well-tolerated and has no significant adverse events.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The adverse reactions in Table 1 below were observed in clinical trials in primary biliary cirrhosis with 180 patients (89 randomized to ursodiol treatment, 91 to placebo treatment). Adverse events are reported regardless of attribution to the test medication. Adverse reactions occurring at a rate of 1% or higher in the ursodiol group, and that are higher than placebo are included in Table 1. Diarrhea and thrombocytopenia at 12 months, nausea/vomiting, fever and other side effects are not included, because they occurred at the same rate or a lower rate than placebo.

Table 1: Adverse events with a frequency ≥ 1% Observed in a Clinical Trial of 180 patients

Adverse event (ordered by MedDRA System Organ Class)		Visit at 12 Months		Visit at 24 Months	
		UDCA[1] n (%)	Placebo n (%)	UDCA[1] n (%)	Placebo n (%)
Blood and lymphatic system disorders	Leukopenia	-	-	2 (2.63)	-
Gastrointestinal disorders	Diarrhea	-	-	1 (1.32)	-
	Peptic ulcer	-	-	1 (1.32)	-
Investigations	Blood creatinine increased	-	-	1 (1.32)	-
	Blood glucose increased	1 (1.18)	-	1 (1.32)	-
Skin and subcutaneous tissue disorders	Rash	-	-	2 (2.63)	-

[1] UDCA=Ursodeoxycholic acid=Ursodiol
Note: Those AEs occurring at the same or higher incidence in the placebo as in the UDCA group have been deleted from this table (this includes diarrhea and thrombocytopenia at 12 months, nausea/vomiting, fever and other toxicity).

In a randomized, cross over study in sixty PBC patients, four patients experienced one serious adverse event each (diabetes mellitus, breast nodule, and fibrocystic breast disease (2 patients)). No deaths occurred in the study. Forty-three patients (43/71.7%) experienced at least one treatment-emergent adverse event (TEAEs) during the study. The most common (defined as ≥5%) TEAEs were asthenia, (11.7%), dyspepsia (10%), edema peripheral (8.3%), hypertension (8.3%), nausea (8.3%), GI disorders (5%), chest pain (5%), and pruritus (5%). These nine TEAEs included abdominal pain and asthenia (1 patient), nausea (3 patients), dyspepsia (2 patients), and anorexia and esophagitis (1 patient each). One patient on the BID regimen (total dose 1000 mg) withdrew due to nausea. All of these nine TEAEs except esophagitis were observed with the BID regimen at a total daily dose of 1000 mg or greater.

Table 2: Treatment-Emergent Adverse Events (TEAEs) with a Frequency of ≥ 1 % Observed in a Clinical Trial of 60 PBC patients

Adverse event (ordered by MedDRA System Organ Class)		TEAEs, n (%)
Blood and lymphatic system disorders	Anemia	1 (1.7)
	Lymphadenopathy	2 (3.3)
Cardiac disorders	Arrhythmia	2 (3.3)
	Cardiovascular disorder	2 (3.3)
Ear and labyrinth disorders	Deafness	1 (1.7)
	Vertigo	1 (1.7)
Eye disorders	Cataract	2 (3.3)
	Eye disorder	1 (1.7)
	Retinal disorder	1 (1.7)
Gastrointestinal disorders	Abdominal pain	2 (3.3)
	Diarrhea	2 (3.3)
	Dyspepsia	6 (10)
	Dysphagia	1 (1.7)
	Esophagitis	1 (1.7)
	Flatulence	1 (1.7)
	Gastrointestinal disorder	3 (5.0)
	Nausea	5 (8.3)
	Salivary gland enlargement	1 (1.7)
	Stomach ulcer	1 (1.7)
General disorders and administration site conditions	Asthenia	7 (11.7)
	Chest pain	3 (5.0)
	Chest pain substernal	1 (1.7)
	Cyst	1 (1.7)
	Edema	5 (8.3)
	Edema generalized	1 (1.7)
	Edema peripheral	5 (8.3)
	Granuloma	1 (1.7)
	Hemorrhagic ulcer	1 (1.7)
	Pain	1 (1.7)
Hepatobiliary disorders	Biliary pain	1 (1.7)
Immune system disorders	Amyloidosis	1 (1.7)
Infections and infestations	Bronchitis	1 (1.7)
	Cystitis	1 (1.7)
	Herpes simplex	1 (1.7)
	Infection	1 (1.7)
	Otitis media	1 (1.7)
	Pharyngitis	1 (1.7)
	Pneumonia	1 (1.7)
	Rhinitis	2 (3.3)
	Urinary tract infection	1 (1.7)
	Vaginitis	1 (1.7)
Metabolism and nutrition disorders	Anorexia	1 (1.7)
	Diabetes mellitus	2 (3.3)
Musculoskeletal and connective tissue disorders	Back pain	1 (1.7)
	Bone disorder	1 (1.7)
	Bone fracture spontaneous	1 (1.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast neoplasm	1 (1.7)
	Lung nodule	1 (1.7)
	Plantar warts	1 (1.7)

Adverse event (ordered by MedDRA System Organ Class)		TEAEs, n (%)
Nervous system disorders	Dizziness	2 (3.3)
	Headache	1 (1.7)
	Migraine	1 (1.7)
	Paresthesia	1 (1.7)
Reproductive system and breast disorders	Breast nodule	1 (1.7)
	Fibrocystic breast disease	2 (3.3)
	Menorrhagia	1 (1.7)
Respiratory, thoracic and mediastinal disorders	Dyspnea	1 (1.7)
	Lung disorder	1 (1.7)
	Respiratory disorder	1 (1.7)
	Sore nose	2 (3.3)
Skin and subcutaneous tissue disorders	Acne	2 (3.3)
	Miliaria	1 (1,7)
	Pruritus	3 (5.0)
	Psoriasis	1 (1.7)
	Rash	1 (1.7)
	Skin disorder	2 (3.3)
	Skin hypertrophy	1 (1.7)
Vascular disorders	Hypertension	5 (8.3)

Less Common Clinical Trial Adverse Drug Reactions (≤1%)

Analysis of the data in the trial with 180 patients (Table 1) revealed no reports of adverse events at rates <1 % with the exception of those adverse events that occurred at the same or at a higher incidence in the treatment group than placebo. No data for TEAEs occurring at rates <1 % in the trial of 60 patients (Table 2) are available due to the small sample size.

Abnormal Hematologic and Clinical Chemistry Findings

In the placebo-controlled trial with 180 patients, change from baseline in hematologic parameters and non-hepatic clinical chemistry were analyzed. Statistically significant differences from baseline are reported in Tables 3 and 4.

Table 3: Hematologic Parameters: Changes from Baseline

		Baseline		Endpoint		Change from Baseline	
		UDCA	Placebo	UDCA	Placebo	UDCA (± SD)	Placebo (± SD)
WBC	Mean (± SD)	5.9 (2.0)	6.2 (4.1)	5.5 (1.6)	5.8 (2.4)	0.5** (1.4)	-0.5 (4.3)
	n	88	87	83	75		
Platelets	Mean (± SD)	238.5 (92.5)	245.4 (112.4)	211.2 (87.2)	223.9 (94.3)	29.4** (39.3)	-17.7* (58.0)
	n	86	86	82	74		

* Statistically different from zero, $p < 0.05$
**Statistically different from zero, $p < 0.01$

There was a significant decrease ($p<0.01$) in WBC and platelets in the UDCA-treated group from baseline and a significant ($p<0.05$) decrease in platelets in the placebo group. There was no significant change in haemoglobin.

Table 4: Clinical Chemistries: Changes from Baseline

		Baseline		Endpoint		Change from Baseline	
		UDCA	**Placebo**	**UDCA**	**Placebo**	**UDCA (± SD)**	**Placebo (± SD)**
Calcium (mg/dL)	Mean (± SD)	9.49[a] (0.40)	9.47 (0.40)	9.39 (0.43)	9.30 (0.51)	-0.12**[,a] (0.37)	-0.19** (0.37)
	n	89	91	83	76		
Cholesterol (mg/dL)	Mean (± SD)	287.73[a] (121.12)	276.03 (105.22)	223.53 (56.80)	261.46 (83.53)	-67.39**[,b] (93.31)	-11.32* (47.70)
	n	89	91	83	76		
Creatinine (mg/dL)	Mean (± SD)	0.86 (0.19)	0.84 (0.21)	0.92 (0.19)	0.92 (0.26)	0.07**[a] (0.18)	0.07** (0.23)
	n	89	91	83	76		
Total Thyroxine (μg/dL)	Mean (± SD)	8.66[a] (1.63)	8.60 (2.27)	7.96 (1.87)	8.27 (3.25)	-0.69*[,a] (1.52)	-0.49 (2.52)
	n	87	90	83	74		
Triglycerides (mg/dL)	Mean (± SD)	102.82[a] (49.25)	117.11 (70.57)	114.18 (55.13)	121.52 (57.56)	11.76*[,a] (44.38)	3.00 (56.74)
	n	88	89	83	75		

** Statistically different from zero, $p < 0.01$
* Statistically different from zero, $p < 0.05$
[a] p = ns, UDCA versus placebo
[b] $p = 0.0001$, UDCA versus placebo

All the non-hepatic clinical chemistries at baseline were not significantly different ($p>0.05$) between the UDCA- and placebo- treated groups. In the UDCA group there was a significant ($p>0.05$) decrease from baseline in calcium, cholesterol and total thyroxine and a significant increase ($p>0.05$) in creatinine and triglycerides. In the placebo group there was a significant ($p>0.05$) decrease in cholesterol and significant increase ($p>0.05$) in calcium and creatinine. There was no significant change seen for sodium, potassium, phosphorus, HDL, and AMA.

Post-Market Adverse Drug Reactions

The following adverse reactions, presented by system organ class in alphabetical order, have been identified during postapproval use of ursodiol. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Blood and lymphatic system disorders*: anemia, eosinophilia, leukopenia, neutropenia, thrombocytopenia.

- *Cardiac disorders*: palpitations.
- *Gastrointestinal disorders*: abdominal discomfort, abdominal pain, cheilitis, constipation, diarrhea, dyspepsia, nausea, vomiting.
- *General disorders and administration site conditions*: malaise, peripheral edema, pyrexia.
- *Hepatobiliary disorders:* decompensated cirrhosis, hepatic failure, hepatic function abnormal
- *Immune system disorders*: angioedema and laryngeal edema, drug hypersensitivity to include facial edema, urticaria.
- *Investigations*: blood glucose increased, blood urine present, weight decreased, weight increased.
- *Musculoskeletal and connective tissue disorders*: myalgia
- *Nervous system disorders*: dizziness, headache.
- *Respiratory, thoracic and mediastinal disorders*: cough, interstitial lung disease.
- *Skin and subcutaneous tissue disorder*: alopecia, dermatitis exfoliative, erythema, lichenoid keratosis, photosensitivity reaction, pruritus, rash.

DRUG INTERACTIONS

Overview

Bile acid sequestering agents may interfere with the action of ursodiol by reducing absorption. Aluminum based antacids adsorb bile acids *in vitro* and may act in the same manner as sequestering agents, thereby interfering with the action of ursodiol. Ursodiol has been shown to be an inducer of CYP3A however the clinical relevance is not known. Metabolic interactions with compounds metabolized by cytochrome P4503A are to be expected**.**

Drug-Drug Interactions

Table 5: Drug-Drug Interactions

	Effect	Clinical comment
Bile acid sequestrants (i.e. cholestyramine or cholestipol)	Reduces ursodiol absorption	May interfere with the action ursodiol
Aluminum based antacids	Reduces ursodiol absorption Adsorbs bile acid *in vitro*	May be expected to interfere with ursodiol
Cytochrome P4503A substrates cyclosporine, nitrendipine and dapsone	Metabolic interaction.	Metabolic interactions with compounds metabolized by cytochrome P4503A are to be expected.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations
Patient Monitoring: Liver function tests (γ-GT, alkaline phosphatase, AST, ALT) and bilirubin levels should be monitored every month for three months after start of therapy, and then every six months. Serum levels of these parameters usually decrease rapidly, thus, demonstrating efficacy. Treatment should be discontinued if the levels of the above parameters increase.

Recommended Dose
The recommended adult dosage for Dom-URSODIOL C (ursodiol) in the treatment of PBC is 13 mg/kg/day to 15 mg/kg/day administered in two to four divided doses with food.

Missed Dose
If you miss a dose, take the missed dose as soon as you remember. If it is almost time for your next dose, skip the dose you missed and take your next regularly scheduled dose. Do not take a double dose.

OVERDOSAGE

Accidental or intentional overdosage with ursodiol has not been reported. The most severe manifestation of overdosage would likely consist of diarrhea that should be treated symptomatically.

Symptoms of acute toxicity in animal studies were salivation and vomiting in dogs, and ataxia, dyspnea, ptosis, agonal convulsions and coma in hamsters.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Ursodiol, a naturally occurring hydrophilic bile acid, derived from cholesterol, is present as a minor fraction of the total human bile acid pool. Oral administration of ursodiol increases this fraction in a dose related manner, to become the major biliary acid, replacing/displacing toxic concentrations of endogenous hydrophobic bile acids that tend to accumulate in cholestatic liver disease.

Multiple mechanisms of action at the cellular and molecular level in addition to the replacement and displacement of toxic bile acids include cytoprotection of the injured bile duct epithelial cells (cholangiocytes) against toxic effects of bile acids, inhibition of apotosis of hepatocytes, immunomodulatory effects via a number of mechanisms including decreasing expression of MHC class I proteins on hepatocytes and cholangiocytes, and stimulation of bile secretion by hepatocytes and cholangiocytes.

The cholesterol-lowering effect observed following the administration of ursodiol in patients with primary biliary cirrhosis could be related to an improvement of cholestasis, modifications in cholesterol metabolism, or both. Changes in the endogenous bile acid composition induced by ursodiol might be the common denominator of these two mechanisms.

Pharmacodynamics

During chronic administration, ursodiol becomes a major biliary and plasma bile acid. At a chronic dose of 13-15 mg/kg/day, ursodiol constitutes 30-50% of biliary and plasma bile acids.

Pharmacokinetics

Absorption: Ursodiol (UDCA) is normally present as a minor fraction of the total bile acids in humans (about 5%). Following oral administration, the majority of ursodiol is absorbed by passive diffusion and its absorption is incomplete.

Distribution: In healthy subjects, at least 70% of ursodiol (unconjugated) is bound to plasma protein. No information is available on the binding of conjugated ursodiol to plasma protein in healthy subjects or primary biliary cirrhosis (PBC) patients. However, since the efficacy of ursodiol is related to its concentration in bile rather than in plasma, serum levels are not indicative of bioavailability in clinical settings. Its volume of distribution has not been determined, but is expected to be small since the drug is mostly distributed in the bile and small intestine. In bile, UDCA concentration reaches a peak in 1-3 hours.

Metabolism: Once absorbed, ursodiol undergoes hepatic extraction to the extent of about 70% in the absence of liver disease. This leads to low blood levels in the systemic circulation. As the severity of liver disease increases, the extent of extraction decreases. In the liver, ursodiol is conjugated with glycine or taurine, then secreted into bile. These conjugates of ursodiol are absorbed in the small intestine by passive and active mechanisms. The conjugates can also be deconjugated in the ileum by intestinal enzymes, leading to the formation of free ursodiol that can be reabsorbed and reconjugated in the liver. Nonabsorbed ursodiol passes into the colon where it is mostly 7-dehydroxylated to lithocholic acid. Some ursodiol is epimerized to chenodiol (CDCA) via a 7-oxo intermediate. Chenodiol also undergoes 7-dehydroxylation to form lithocholic acid. These metabolites are poorly soluble and excreted in the feces. A small portion of lithocholic acid is reabsorbed, conjugated in the liver with glycine or taurine, and sulfated at the 3 position. The resulting sulfated lithocholic acid conjugates are excreted in bile and then lost in feces.

Lithocholic acid, when administered chronically to animals, causes cholestatic liver injury that may lead to death from liver failure in certain species unable to form sulfate conjugates. Ursodiol is 7-dehydroxylated more slowly than chenodiol. For equimolar doses of ursodiol and chenodiol,

steady state levels of lithocholic acid in biliary bile acids are lower during ursodiol administration than with chenodiol administration. Humans and chimpanzees can sulfate lithocholic acid. Although liver injury has not been associated with ursodiol therapy, a reduced capacity to sulfate may exist in some individuals. Nonetheless, such a deficiency has not yet been clearly demonstrated and must be extremely rare, given the several thousand patient-years of clinical experience with ursodiol.

Excretion: Ursodiol is excreted primarily in the feces. With treatment, urinary excretion increases, but remains less than 1%, except in severe cholestatic liver disease.

STORAGE AND STABILITY

Dom-URSODIOL C tablets should be stored between 15°C and 30°C in a closed container.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Availability of Dosage Forms

250 mg Tablet:
Dom-URSODIOL C is available as white, elliptical, biconvex, coated tablet debossed with “250" on one side and “P” logo on the other, in strength of 250 mg. Available in bottles of 100 and 500 tablets.

500 mg Tablet:
Dom-URSODIOL C is available as white, elliptical, biconvex, coated tablet debossed with “500" on one side and “P” logo on the other, in strength of 500 mg. Available in bottles of 100 tablets.

Composition

Dom-URSODIOL C Tablets contain the following non-medicinal ingredients: hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, sodium starch glycolate.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

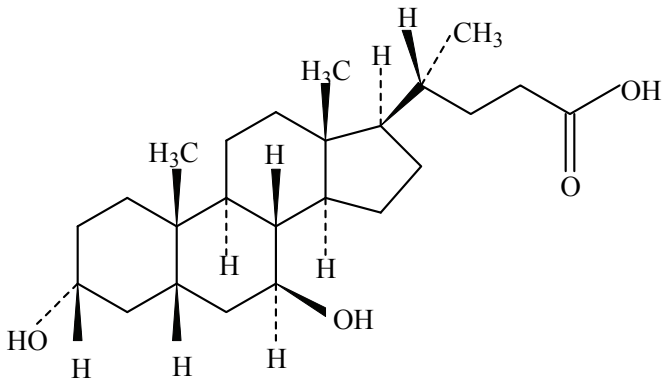
Proper name: Ursodiol

Chemical name: 3α, 7β-dihydroxy-5β-cholan-24-oic acid

Molecular formula and: $C_{24}H_{40}O_4$

Molecular mass: 392.6 g/mol

Structural formula:



Physicochemical properties:

Description: Ursodiol is a naturally occurring bile acid in man. Ursodiol is a bitter-tasting, white, crystalline powder.

Solubility: Ursodiol is practically insoluble in water, freely soluble in alcohol and glacial acetic acid, slightly soluble in chloroform, and very slightly soluble in ether.

Melting Range: 200°C - 205°C

pKa: 6.0

pH: Alkaline

CLINICAL TRIALS

Comparative Bioavailability Studies

Single-Dose Crossover Comparative Bioavailability Study of Dom-URSODIOL C 2 x 250 mg Tablets, was performed *versus* Axcan Pharma Inc., URSO 2 x 250 mg Tablets, Administered as 2 x 250 mg Tablet in Healthy Subjects Under Fasting Conditions. Bioavailability data were measured and the results are summarized in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA
Ursodiol (2 X 250 mg)
From measured ursodiol data (corrected for baseline)
Geometric Mean
Arithmetic Mean (CV %)

Parameter	Test Dom-URSODIOL C	Reference URSO®†	% Ratio of Geometric Means	90% Confidence Interval	
				LOWER	UPPER
AUC_T (ng.h/mL)	13073.3 13662.1 (31.9)	13552.5 14934.3 (51.7)	96.46	83.3	111.71
AUC_I (ng.h/mL)	14061.8 15036.8 (34.2)	12871.9 14120.3 (37.0)	109.24	94.2	126.69
C_{MAX} (ng/mL)	3299.5 3393.3 (25.3)	3440.2 3597.5 (29.1)	95.91	83.53	110.12
T_{MAX}* (h)	2.00 (66.2)	2.50 (98.6)	---	---	---
$T_{½}$* (h)	7.18 (45.1)	7.96 (52.0)	---	---	---

* expressed as arithmetic mean (CV%) only
† URSO® is manufactured by Axcan Pharma Inc. and was purchased in Canada.

Study demographics and trial design:

Table 6: Summary of patient demographics for clinical trials in primary biliary cirrhosis (PBC)

Study	Trial design	UDCA[1] Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range) (years)	Gender
US Study	multicenter, randomized, double-blind, placebo-controlled	13-15 mg/kg/day, administered in 4 divided doses (n=89), or placebo (n=91), 2 years	180 patients with PBC	UCDA: 53.6 (±9.5) placebo: 51.5 (±9.3)	UCDA: 7 M/89 F placebo: 12 M/91 F
Canadian Study	randomized, double- blind, placebo controlled	14 mg/kg/day (n=111), or placebo (n= 111), 2 years	222 patients with PBC	UCDA: 57.3 placebo: 55.4	UCDA: 10 M/111 F placebo: 6 M/111 F
Multinational Study	multicenter, multinational (France-Canada), double-blind, placebo controlled	13-15 mg/kg/day (n=72), or placebo (n=73), 2 years	145 patients with histologically confirmed biliary cirrhosis	UCDA: 55 (±1) placebo: 57 (±1)	UCDA: 4 M/72 F placebo: 8 M/73 F

[1] UDCA = Ursodeoxycholic acid = Ursodiol = URSO®

U.S. Study: A multicenter, randomized, double-blind, placebo-controlled study was conducted to evaluate the efficacy of ursodeoxycholic acid at a dose of 13-15 mg/kg/day, administered in 4 divided doses in 180 patients with PBC. Upon completion of the double-blind portion, all patients entered an open-label, active treatment, extension phase.

Treatment failure, the main efficacy end point measured during this study, was defined as death, need for liver transplantation, histologic progression by two stages or to cirrhosis, development of varices, ascites or encephalopathy, marked worsening of fatigue or pruritus, inability to tolerate the drug, doubling of serum bilirubin and voluntary withdrawal. After two years of double-blind treatment, the incidence of treatment failure was significantly reduced in the ursodiol group (n=89) as compared to the placebo group (n=91). Time to treatment failure was also significantly delayed in the ursodiol treated group, regardless of either histologic stage or baseline bilirubin levels (>1.8 or ≤1.8 mg/dL).

Using a definition of treatment failure which excluded doubling of serum bilirubin and voluntary withdrawal, time to treatment failure was significantly delayed in the ursodiol group. In comparison with placebo, treatment with ursodiol resulted in a significant improvement in the following serum hepatic biochemistries when compared to baseline: total bilirubin, AST, alkaline phosphatase and IgM.

Canadian Study: A second study conducted in Canada randomized 222 PBC patients to ursodiol 14 mg/kg/day (n=111) or placebo (n=111), in a double-blind manner during a two-year period. At two years, a statistically significant difference between the two treatments, in favor of ursodiol, was demonstrated by the following: reduction in the proportion of patients exhibiting a more than 50%

increase in serum bilirubin; median percent decrease in bilirubin, transaminases and alkaline phosphatase, incidence of treatment failure, and time to treatment failure. The definition of treatment failure included: discontinuing the study for any reason, a total serum bilirubin level greater than or equal to 1.5 mg/dL or increasing to a level equal to or greater than two times the baseline level, and the development of ascites or encephalopathy.

Evaluation of patients at 4 years or longer was inadequate due to the high drop out rate and small number of patients. Therefore, death, need for liver transplantation, histological progression by two stages or to cirrhosis, development of varices, ascites or encephalopathy, marked worsening of fatigue or pruritus, inability to tolerate the drug, doubling of serum bilirubin and voluntary withdrawal were not assessed.

Multinational Study: A two-year multicenter, multinational (France-Canada), double-blind study was conducted to compare the efficacy of ursodiol versus placebo in primary biliary cirrhosis. Patients with histologically confirmed biliary cirrhosis were randomized to receive either ursodiol 13-15 mg/kg/day (n=72), or placebo (n=73). Treatment failure was defined as a doubling of bilirubin levels (>70 μmol/L) or the occurrence of severe complications (ascites or variceal bleeding) or an adverse event.

The results showed that treatment failed in six patients in the ursodiol group, as compared with thirteen in the placebo group ($p<0.01$). A single patient in each group withdrew because of minor adverse effects. After two years of treatment, the proportion of patients with clinically overt disease decreased only in the ursodiol group ($p<0.02$). The patients treated with ursodiol had significant improvements in serum levels of bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, cholesterol, and IgM (all $p<0.01$); the antimitochondrial antibody titer ($p<0.01$); and the Mayo risk score ($p<0.001$). In a follow-up analysis of 95 liver-biopsy specimens, only the group receiving ursodiol showed a significant improvement in the mean histologic score ($p<0.002$) and in all the characteristic histologic features except fibrosis.

At the end of this trial, all patients received ursodiol (13-15 mg/kg/day) and were monitored for an additional two years, using the same criteria.

After four years, the overall treatment failure rate was 12% in the ursodiol group and 26% in the original placebo group ($p<0.001$). Two patients in the ursodiol group had undergone a liver transplantation, compared to 12 in the original placebo group ($p<0.001$). Survival was similar in the two groups: 5 deaths (various causes) occurred in the ursodiol group and 7 in the original placebo group.

Combined Analysis: The raw data from the above three studies have been combined in order to estimate, at four years, the magnitude of the effect of ursodiol treatment on survival free of transplant, defined as time to transplant, or death without transplant.

In these studies, all patients had histologically confirmed, antimitochondrial antibody positive, primary biliary cirrhosis. They were randomized to receive ursodiol (13-15 mg/kg/day) or identical placebo. In one study, blinded randomization continued for four years. In two studies, open label ursodiol was offered to all patients after two years. The endpoint of survival free of liver transplant

was compared between the ursodiol and placebo groups using standard life table analyses. Analyses were done on an "intent-to-treat" basis. The risk reduction was calculated in order to define the magnitude of the benefit from ursodiol treatment.

A total of 548 patients were randomized in these studies: 273 received ursodiol and 275, the placebo. Baseline characteristics were comparable at entry in both groups. Median length of follow-up was four years in the ursodiol group, and 3.8 years in the original placebo group. Placebo patients who received ursodiol did so for a mean of one year. There were 47 patients in the ursodiol group and 68 in the placebo group who did not survive nor needed a liver transplant. Survival free of transplantation was extended in patients originally randomized to ursodiol when compared to those on placebo (mean of 3.66 versus 3.45 years, p=0.014). In the ursodiol group the risk of dying or being transplanted was reduced by 32% (± 11%) of that observed in the original placebo group.

Unapproved High-Dose Ursodeoxycholic Acid for the Treatment of Primary Sclerosing Cholangitis: In a recent Clinical Trial (Lindor *et al*., 2009), one hundred fifty adult patients with PSC were enrolled in a long-term, randomized, double-blind controlled trial of high-dose (28-30 mg/kg/day – 1.5 to 2.0fold the recommended dose) versus placebo. Liver biopsy and cholangiography were performed before randomization and after 5 years. The primary outcome measures were development of cirrhosis, varices, cholangiocarcinoma, liver transplantation, or death. The study was terminated after 6 years due to futility. During therapy, aspartate aminotransferase and alkaline phosphatase levels decreased more in the ursodeoxycholic acid group than the placebo group ($P < 0.01$), but improvements in liver function tests were not associated with decreased endpoints. By the end of the study, 30 patients in the ursodeoxycholic acid group (39%) versus 19 patients in the placebo group (26%) had reached one of the pre- established clinical endpoints. The risk was 2.1 times greater for death and transplantation in the ursodeoxycholic acid group versus the placebo group ($P = 0.038$). Serious adverse events were more common in the ursodeoxycholic acid group than the placebo group (63% versus 37% [$P \leq 0.01$]). Long-term, high-dose ursodeoxycholic acid therapy was associated with improvement in serum liver function tests in PSC but did not improve survival and was associated with higher rates of serious adverse events.

DETAILED PHARMACOLOGY

Administration of ursodiol to rats, rabbits, hamsters and dogs produced modification of bile composition. Bile flow increased as did total bile acid output. In the liver, ursodiol decreased HMG-CoA reductase activity and cholesterol 7-hydroxylase activity. Triglyceride, phospholipid and cholesterol synthesis were decreased.

Studies have demonstrated that ursodiol acts on the hepatic cells and plays a role in the bile acid dependent mechanism of bile formation. Its choleretic activity results from its osmotic activity as well as its stimulating effect on organic ion transport (probably HCO_3).

In vitro studies showed that tauroursodeoxycholic acid (i.e. in the liver ursodiol is conjugated with taurine or glycine) decreased cholesterol uptake in rat jejunal membranes by an unknown

mechanism. When ursodiol was perfused into the liver of rats or baboons, bile flow either remained unchanged or increased, bile acid and phospholipid outputs were increased, while cholesterol specific activity was decreased. Tauroursodeoxycholic acid caused only little output of plasma membrane enzyme concentration (5-nucleotidase and alkaline phosphatase), which may represent a characteristic difference between the effects of chenodiol and ursodiol on the hepatobiliary system.

Ursodiol produced minimal or no effect on water and sodium excretion from the GI tract of rats and rabbits. It induced less damage to the GI tract mucosa than chenodiol. These observations correlate well with the clinical findings that diarrhea is infrequent with ursodiol.

Ursodiol lowered blood sugar levels in mice, and increased the volume of pancreatic secretion in rabbits, thus suggesting a stimulatory effect of ursodiol on the pancreas.

At therapeutic doses, ursodiol uncouples the normal relationship between cholesterol, phospholipids and bile acid secretion. Ursodiol inhibits cholesterol absorption in the gut, thereby, reducing cholesterol output into the bile. It further reduces cholesterol secretion into bile. These actions contribute to biliary cholesterol desaturation.

TOXICOLOGY

Acute Toxicity

Results from various studies indicated that oral, subcutaneous, intraperitoneal and intravenous administration of ursodiol in mice, rats, hamsters, and dogs at single doses of 1.21 to 10 g/kg over a seven-day observation period, did not cause any deaths in any of the species used. For mice and dogs, the LD_{50} was >10 g/kg, and rats had an LD_{50} over >5 g/kg. Hamsters were found to be more sensitive than rats and dogs as the LD_{50} for this species was calculated to be >3.16 g/kg.

No significant sex difference was seen. Toxic signs observed included: inhibition of motility, CNS toxicity such as ataxia and sedation, GI tract disturbances such as vomiting, salivation, decreased body weight and appetite.

Subacute Toxicity

Two short-term toxicological studies were conducted in rats. Ursodiol was administered orally at a daily dose of 0.5 to 4.0 g/kg/day for five weeks or alternatively at doses of 0.0625 to 0.5 g/kg daily for five weeks by the intraperitoneal route.

No deaths occurred in the study with oral administration of ursodiol, whereas, one male and one female rat died in the 0.25 g/kg group, and six males and four females died in the 0.5 g/kg group of the study in which ursodiol was administered by the intraperitoneal route. The most marked autopsy findings were dilation and adhesion of intraperitoneal organs. As these became gradually more severe, retention of ascites and renal abscesses appeared. It was concluded that 0.0625 g/kg was the safe dose and 0.125 g/kg was near the maximum tolerable dose.

Ursodiol orally administered to rats did not cause any clinical symptoms or any changes in laboratory parameters

Chronic Toxicity
Four long-term toxicity studies were performed in rats and monkeys. The results of these studies are summarized below.

Rat Study: In one study, ursodiol was administered orally to Sprague-Dawley rats for 26 weeks. The dosage varied between 0.1 and 2.5 g/kg/day and various observations were performed daily.

No deaths occurred during the experimental period. Lower doses (0.1 and 0.5 g/kg) were well tolerated. However, a 2.5 g/kg dose of ursodiol resulted in significant reduction of body weight gain and food intake. No significant changes were seen in laboratory findings and clinical observations.

In the second study, male Wistar rats were given 0.5 to 4.0 g/kg of ursodiol orally for 26 consecutive weeks and a variety of observations were made.

The results indicated a decrease in body weight gain and an increase in water intake in the 4.0 g/kg dosage group. Eight rats (four at the high dose level) died during the experiment. The cause of death was attributed to pathological changes in the lung and intestine. Laboratory findings revealed no abnormal changes that might be ascribed to drug administration.

Monkey study: A 26-week study was performed in Rhesus monkeys. Ursodiol at doses of 0.04 and 0.10 g/kg/day were given orally.

No deaths occurred during the treatment period. There were no abnormalities in the laboratory parameters.

In a 52-week study, ursodiol at a dose of 0.05 to 0.9 g/kg was administered to Rhesus monkeys. The animals were observed daily for various clinical signs and symptoms. They were weighed weekly, blood and urine was collected and examined every three months. After 52 weeks, the animals were sacrificed and an autopsy was performed.

Three animals belonging to the 0.90 g/kg group, two in the 0.30 g/kg group and one in the 0.10 g/kg died during the study. These deaths were considered to be related to ursodiol. Liver toxicity (small round-cell infiltration, vacuolar degeneration, necrosis of hepatic cells, phagocytosis and hepatic abscess) and thickening of the alveolar wall of the lungs was observed in deceased animals from all groups. Necrosis of the stomach wall was observed in deceased animals from the 0.90 g/kg group. A regression of body weight gain was seen in the 0.30 and 0.90 g/kg groups. Episodes of diarrhea were observed in all groups including the control group. No remarkable changes were noted in hematological, urinary, electrographic, blood pressure and ocular fundi examinations. However, serum SGPT, AST and ALP increased significantly.

From the above findings, it was concluded that ursodiol, when administered at daily doses exceeding 0.10 g/kg, caused hepatotoxicity in Rhesus monkeys.

Carcinogenicity
In two 24-month oral carcinogenicity studies in mice, ursodiol at doses up to 1,000 mg/kg/day (3,000 mg/m^2/day) was not tumorigenic. Based on body surface area, for a 50 kg person of average height (1.46 m^2 body surface area), this dose represents 5.4 times the recommended maximum clinical dose of 15 mg/kg/day (555 mg/m^2/day).

In a two-year oral carcinogenicity study in Fischer 344 rats, ursodiol at doses up to 300 mg/kg/day (1,800 mg/m^2/day, 3.2 times the recommended maximum human dose based on body surface area) was not tumorigenic.

In a life-span (126-138 weeks) oral carcinogenicity study, Sprague-Dawley rats were treated with doses of 33 to 300 mg/kg/day, 0.4 to 3.2 times the recommended maximum human dose based on body surface area. Ursodiol produced a significantly ($p < 0.5$, Fisher's exact test) increased incidence of pheochromocytomas of the adrenal medulla in females of the highest dose group.

In 103-week oral carcinogenicity studies of lithocholic acid, a metabolite of ursodiol, doses up to 250 mg/kg/day in mice and 500 mg/kg/day in rats did not produce any tumors. In a 78-week rat study, intrarectal instillation of lithocholic acid (1 mg/kg/day) for 13 months did not produce colorectal tumors. A tumor-promoting effect was observed when it was administered after a single intrarectal dose of a known carcinogen N-methyl-N'-nitro-N-nitrosoguanidine. On the other hand, in a 32-week rat study, ursodiol at a daily dose of 240 mg/kg (1,440 mg/m^2, 2.6 times the maximum recommended human dose based on body surface area) suppressed the colonic carcinogenic effect of another known carcinogen, azoxymethane.

Mutagenicity
Ursodiol was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y, $TK^{+/-}$) forward mutation test, the human lymphocyte sister chromatid exchange test, the mouse spermatogonia chromosome aberration test, the Chinese hamster micronucleus test and the Chinese hamster bone marrow cell chromosome aberration test.

Reproduction and Teratology
Ursodiol did not show any teratogenic effect in mice, rats and rabbits at oral dose levels up to 1.5, 4.0 and 0.3 g/kg, respectively, and in mice and rats at intraperitoneal dose levels up to 0.2 g/kg. Furthermore, it did not influence mating performance and fertility, except in one study where these parameters were slightly reduced in female rats receiving 2.0 g/kg. Breeding capacity was not altered by the administration of ursodiol.

Oral administration of 1.5 g/kg in mice and 2.0 g/kg in rats induced a decrease in maternal weight gain and lower mean weights of live fetuses. In addition, the number of resorption sites was increased in rats at a dose of 2.0 g/kg. Rabbits were much more sensitive than mice and rats to the toxic action of ursodiol. The administration of doses of 0.1 g/kg and greater caused a decrease in

food consumption, maternal body weight gain and motor activity as well as an increase in resorption sites, and absorption death.

Intraperitoneal administration of 0.2 g/kg ursodiol to mice and rats induced a decrease in maternal body weight gain, low fetal weight and an increase of resorption sites.

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44. Product Monograph: URSO® and URSO DS™ (Ursodiol USP) by Aptalis Pharma Canada Inc. Date of Revision: November 2, 2011, Control #150620.

PART III: CONSUMER INFORMATION

[Pr]Dom-URSODIOL C
Ursodiol Tablets USP

This leaflet is part III of a three-part "Product Monograph" and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Dom-URSODIOL C, contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Dom-URSODIOL C has been prescribed for you by your physician for the management of cholestatic liver disease.
Dom-URSODIOL C is only available by prescription.

What it does:
Ursodiol is a naturally occurring bile acid found in small quantities in normal human bile.

In patients with cholestatic liver disease the release and flow of bile through the bile ducts are reduced. By taking Dom-URSODIOL C the amount of ursodiol in the bile increases, changing the make-up of the bile and causing an increase in bile flow. Ursodiol also works by replacing toxic bile acids that can destroy liver tissue.

When it should not be used:
If you are allergic (hypersensitive) to ursodiol or to any of the non medicinal ingredients (see *what the nonmedicinal ingredients are*)

What the medicinal ingredient is:
Ursodiol

What the non-medicinal ingredients are:
hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, sodium starch glycolate.

What dosage forms it comes in:
Tablets: 250 mg and 500 mg

WARNINGS AND PRECAUTIONS

BEFORE you use Dom-URSODIOL C tell your doctor if:

- You have taken Dom-URSODIOL C before and if it was not well-tolerated or caused an allergy.
- You have liver problems, or are in need of a liver transplant.
- You have variceal bleeding (bleeding from swollen veins, arteries, or lymph vessels).
- You have ascites (swelling in the abdomen).
- You are taking other prescription or non-prescription medicines.
- You are using any new medicine (prescription or non-prescription) such as bile reduction medicines (cholestyramine or colestipol), aluminum based antacids (Rolaids, Maalox, Mylanta, and many others), and cyclosporine, nitrendipine, or dapsone
- You develop any new medical problem while using this medicine.
- You have severe stomach pain.
- You are pregnant, plan to become pregnant, are breast-feeding or plan to breast-feed.
- You need other medical treatment by another doctor, let him or her know that you are taking Dom-URSODIOL C.

Dom-URSODIOL C is not recommended for use in children.

You should discuss with your doctor the benefits and risks of taking Dom-URSODIOL C for your medical condition.

This medication is prescribed for a particular health problem and for your personal use only. Do not give it to another person.

Keep this and all other medicines out of the reach of children.

INTERACTIONS WITH THIS MEDICATION

The following medicines may decrease the amount of ursodiol that is absorbed into your body:

- Medicines that reduce the amount of bile acids such as cholestyramine or colestipol
- Antacids that contain aluminum such as Rolaids, Maalox, Mylanta, and many others.

The absorption and metabolism of the following medicines may be affected by taking ursodiol:

- Cyclosporine
- Dapsone
- Nitrendipine

Use of these medicines with Dom-URSODIOL C may require patients to be closely monitored and the dose of their medicines adjusted.

PROPER USE OF THIS MEDICATION

Usual Adult Dose:

Your doctor would have prescribed the amount of Dom-URSODIOL C you should take each day for your medical condition. Dom-URSODIOL C should be taken in 2 to 4 divided doses with food. It is easier to remember to take your medication, if it is taken at the same time each day. Setting up a routine to take your medication helps this activity become a normal part of your day.

Take Dom-URSODIOL C for the full duration of treatment, even if you begin to feel better.

This medication should only be used as instructed by your doctor. Follow your doctor's instructions. Do not change the dose or stop the treatment without your doctor's advice.

Your doctor will ask you to have regular medical checkups, and will likely require liver tests. It is important to respect the dates proposed.

Overdose:
The most severe symptom of overdosage would likely be diarrhea.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose, take the missed dose as soon as you remember. If it is almost time for your next dose, skip the dose you missed and take your next regularly scheduled dose. Do not take a double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Common >1% and <10%	Anemia		√	
	Dizziness	√		
	Reduced white blood cells in the blood		√	
	Headache	√		
	Diarrhea		√	
	Swelling of the extremities		√	
	Blood glucose increased		√	
	Abdominal pain		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate emergency medical attention
		Only if severe	In all cases	
Unknown	Swelling beneath the skin and Swelling of the throat			√
	Palpitation	√		
	Cough	√		
	Increase in eosinophils in the blood		√	
	Drug hypersensitivity to include facial edema			√
	Decreased blood neutrophils		√	
	Interstitial lung disease			√
	Decreased blood platelets		√	
	Dermatitis exfoliative			√
	Constipation		√	
	Skin redness and Papular skin lesion			√
	Fever		√	
	Photosensitivity reaction			√

HOW TO STORE IT

Dom-URSODIOL C Tablets should be stored between 15°C and 30°C in a closed container.

Keep this and all other medication out of the reach of children.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals, can be obtained by contacting Dominion Pharmacal at 1-888-550-6060.

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