PRODUCT MONOGRAPH

[Pr]pms-URSODIOL C

Ursodiol Tablets, USP

Tablets, 250 mg & 500 mg, Oral

Bile Acid Preparation

PHARMASCIENCE INC.
6111 Royalmount Avenue, Suite 100
Montréal, Québec
H4P 2T2

www.pharmascience.com

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Gastrointestinal	09/2023

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Sections or subsections that are not applicable at the time of authorization are not listed.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

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

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

1.1 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

2 CONTRAINDICATIONS

pms-URSODIOL C is contraindicated in patients:

- who are hypersensitive to ursodiol or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.
- with complete biliary obstruction of extrahepatic origin;
- with widespread intrahepatic obstruction

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

The monitoring of pms-URSODIOL C in the management of cholestatic liver diseases should be based on the biochemical parameters of cholestasis, 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.

Patient Monitoring: Serum 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. Serial monitoring will allow for the early detection of a possible deterioration of the hepatic function. Serum levels of these parameters usually decrease rapidly. Improved serum liver tests (e.g., AST, ALT) do not always correlate with improved disease status. For patients who have a recent history of adequate biochemical response to

the treatment, UDCA discontinuation should be considered when serum liver function tests increase to a level considered clinically significant. See 7 WARNINGS AND PRECAUTIONS).

Caution has to be exercised to maintain the bile flow of the patients taking UDCA.

4.2 Recommended Dose and Dosage Adjustment

The recommended adult dosage for pms-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.

Health Canada has not authorized an indication for pediatric use.

4.4 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.

5 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.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/Strength/ Composition	Nonmedicinal Ingredients
Oral	Tablet / 250 mg & 500 mg	Magnesium Stearate, Microcrystalline Cellulose, Opadry Clear (contains Hydroxypropyl Methylcellulose and Polyethylene Glycol), Polyethylene Glycol, Povidone, Sodium Lauryl Sulfate and Sodium Starch Glycolate.

Availability of Dosage Forms

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

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

7 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 16 NON-CLINICAL TOXICOLOGY).

Gastrointestinal
Bezoars in Patients with Risk for Intestinal Stenosis or Stasis
There have been very rare post-marketing reports of bezoars leading to obstructive symptoms that require surgical interventions in ursodiol-treated patients with medical conditions that predispose to intestinal stenosis or stasis (e.g., surgical enteroanastomoses, Crohn's disease).

Hepatic/Biliary/Pancreatic
Patients with variceal bleeding, hepatic encephalopathy, ascites, or in need of an urgent liver transplant, should receive appropriate specific treatment. Caution should be exercised when UDCA is administered in a setting of partial biliary obstruction of extra-hepatic origin.

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:

Serum 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. Serial monitoring will allow for the early detection of a possible deterioration of the hepatic function. Serum levels of these parameters usually decrease rapidly. Improved serum liver tests (e.g., AST, ALT) do not always correlate with improved disease status. For patients who have a recent history of adequate biochemical response to the treatment, UDCA discontinuation should be considered when serum liver function tests increase to a level considered clinically significant. See 4 DOSAGE AND ADMINISTRATION.

Caution has to be exercised to maintain the bile flow of the patients taking UDCA.

7.1. Special Populations

7.1.1 Pregnant Women

There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, pms-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 fetus. See also 16 NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

8 ADVERSE REACTIONS

8.1 Adverse 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.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The adverse reactions in Table 2 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 2. 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 2: Adverse Events with a Frequency ≥ 1% Observed in a Clinical Trial of 180 Patients

	Visit at 12 Months		Visit at 24 Months	
	UDCA[1] n = [89] (%)	**Placebo n = [91] (%)**	**UDCA[1] n = [89] (%)**	**Placebo n = [91] (%)**
Blood and lymphatic system disorders				
Leukopenia	-	-	2 (2.63)	-
Gastrointestinal				
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 3: Treatment-Emergent Adverse Events (TEAEs) with a Frequency of ≥ 1 % Observed in a Clinical Trial of 60 PBC patients

Adverse Event	TEAEs, n (%)
Blood and Lymphatic System Disorders	
Anemia	1 (1.7)
Lymphadenopathy	2 (3.3)
Cardiovascular	
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	
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)

Adverse Event	TEAEs, n (%)
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)
Plantar warts	1 (1.7)
Lung nodule	1 (1.7)
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	1 (1.7)
Miliaria	1 (1.7)
Pruritus	3 (5.0)
Psoriasis	1 (1.7)

Adverse Event	TEAEs, n (%)
Rash	1 (1.7)
Skin Disorder	2 (3.3)
Skin hypertrophy	1 (1.7)
Vascular Disorders	
Hypertension	5 (8.3)

8.3 Less Common Clinical Trial Adverse Reactions (<1%)

Analysis of the data in the trial with 180 patients (Table 2) 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 3) are available due to the small sample size.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data Clinical Trial 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 Table 4 and Table 5.

Table 4: 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 hemoglobin.

Table 5: 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 (mcg/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.

8.5 Post-Market Adverse Reactions

The following adverse reactions, presented by system organ class in alphabetical order, have been identified during post-approval 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:, eosinophilia, neutropenia, thrombocytopenia.

Cardiac disorders: palpitations.

Gastrointestinal disorders: abdominal discomfort, bezoars cheilitis, constipation, vomiting.

General disorders and administration site conditions: malaise, pyrexia.

Hepatobiliary disorders: jaundice (or aggravation of pre-existing jaundice)

Immune system disorders: angioedema and laryngeal edema, drug hypersensitivity to include facial edema, urticaria.

Investigations: blood urine present, weight decreased, weight increased, ALT increased, AST increased, blood alkaline phosphatase increased, blood bilirubin increased, γ-GT increased, transaminases increased. Rare instances of severe liver injury (elevated values for ALT/AST, ALP, γ-GTP and total bilirubin) have been reported with ursodiol.

Musculoskeletal and connective tissue disorders: myalgia

Respiratory, thoracic and mediastinal disorders: cough, interstitial lung disease.

Skin and subcutaneous tissue disorder: alopecia, dermatitis exfoliative, drug eruption, erythema, lichenoid keratosis, photosensitivity reaction.

9 DRUG INTERACTIONS

9.2 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**.**

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

Table 6: Established or Potential Drug-Drug Interactions

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

Legend: PL - Published Literature

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 apoptosis 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.

10.2 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.

10.3 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.

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

11 STORAGE, STABILITY AND DISPOSAL

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

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

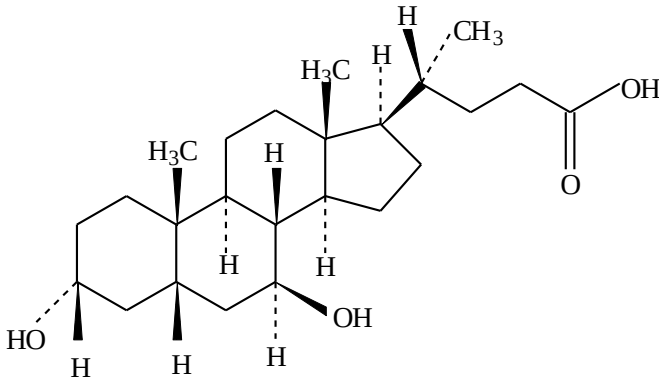
Drug Substance

Proper name: Ursodiol

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

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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Primary Biliary Cirrhosis (PBC)

Table 7: Summary of patient demographics for clinical trials in primary biliary cirrhosis (PBC)

Study	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
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	UDCA: 53.6 (±9.5) placebo: 51.5 (±9.3)	UDCA: 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	UDCA: 57.3 placebo: 55.4	UDCA: 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 histologicall y confirmed biliary cirrhosis	UDCA: 55 (±1) placebo: 57 (±1)	UDCA: 4 M/72 F placebo: 8 M/73 F

[1] UDCA = Ursodeoxycholic acid = Ursodiol

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.

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. 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.

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 mcmol/L) or the occurrence of severe complications (ascites or variceal bleeding) or an adverse event.

Study Results

Table 8: Primary Efficacy Analysis for clinical trials in primary biliary cirrhosis (PBC) – US and Canadian Studies

Primary Endpoint: Treatment failure	
US Study*	
Placebo (n=91) Ursodiol (13-15 mg/kg/day) (n= 89)	• The incidence of treatment failure was significantly reduced in the ursodiol group as compared to the placebo group. • 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). • 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**	
Placebo (n=111) Ursodiol (14 mg/kg/day) (n= 111)	• 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.

Definition of Treatment Failure

***US Study:** Treatment failure 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.

****Canadian Study:** 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.

Table 9: Primary Efficacy Analysis for clinical trials in primary biliary cirrhosis (PBC) – Multinational Study

Multinational Study*			
After 2 years:			
	Ursodiol 13-15 mg/kg/day (n=72)	**Placebo** (n=73)	**p-value**
No. of patients failed treatment:	6	13	p<0.01
After 4 years:			
Treatment failure rate:	12%	26%	p<0.001
Liver transplantation	2 patients	12 patients	p<0.001
Survival	5 deaths	7 deaths	

*Multinational Study: 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.

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.

Table 10: Combined Analysis for clinical trials in primary biliary cirrhosis (PBC)

Combined analysis			
	ursodiol (13-15 mg/kg/day) (n = 273)	Placebo (n = 275)	p-value
Patients who did not survive nor needed a liver transplant*	47	68	-
Survival free of transplantation	3.66 years	3.45 years	p=0.014
Reduction in the risk of dying or being transplanted	32 %	11%	-

Unapproved High-Dose Ursodeoxycholic Acid for the Treatment of Primary Sclerosing Cholangitis

In a recent Clinical Trial, one hundred fifty adult patients with primary sclerosing cholangitis (PSC) were enrolled in a long-term, randomized, double-blind controlled trial of high-dose (28-30 mg/kg/day – 1.5 to 2.0-fold 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. 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*<0.01]). Long-term, high-dose ursodeoxycholic acid therapy in PSC did not improve survival and was associated with higher rates of serious adverse events.

14.2 Comparative Bioavailability Studies

A randomized, two-way, single-dose, crossover comparative bioavailability study of pms-URSODIOL C 250 mg tablets (Pharmascience Inc.) and URSO® 250 mg tablets (Axcan Pharma Inc.) was conducted in healthy, adult, male subjects under fasting conditions. Comparative bioavailability data from 22 subjects that were included in the statistical analysis are presented in the following table:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Ursodiol (2 X 250 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test[1]	Reference[2]	% Ratio of Geometric Means	90% Confidence Interval
AUC_T (ng.h/mL)	13073.3 13662.1 (31.9)	13552.5 14934.3 (51.7)	96.5	83.3 – 111.7
AUC_I (ng.h/mL)	14061.8 15036.8 (34.2)	12871.9 14120.3 (37.0)	109.2	94.2 – 126.7
C_{MAX} (ng/mL)	3299.5 3393.3 (25.3)	3440.2 3597.5 (29.1)	95.9	83.5 – 110.1
T_{MAX}[3] (h)	2.00 (66.2)	2.50 (98.6)		
$T_{1/2}$[3] (h)	7.18 (45.1)	7.96 (52.0)		

[1] pms-IRSODIOL C (ursodiol) tablets, 250 mg (Pharmascience Inc.)
[2] URSO® (ursodiol) tablets, 250 mg (Axcan Pharma Inc.)
[3] Expressed as the arithmetic mean (CV %) only

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General 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.

Reproductive and Developmental Toxicology:
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.

17 SUPPORTING PRODUCT MONOGRAPHS

1. URSO® and URSO DS® (tablets, 250 mg and 500 mg), submission control 268229, Product Monograph, Aptalis Pharma Canada Inc., February 23, 2023.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]pms-URSODIOL C
Ursodiol Tablets

Read this carefully before you start taking **pms-URSODIOL C** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **pms-URSODIOL C**.

What is pms-URSODIOL C used for:
pms-URSODIOL C is used to manage cholestatic liver disease.

How does pms-URSODIOL C work?
pms-URSODIOL C contains ursodiol (ER-so-DYE-all), which is a naturally occurring bile acid found in small quantities in normal human bile.

Cholestatic liver disease is caused when the release and flow of bile through the bile ducts from your liver are reduced. By taking pms-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.

What are the ingredients in pms-URSODIOL C?
Medicinal ingredients: Ursodiol

Non-medicinal ingredients: pms-URSODIOL C contains the following excipients: Magnesium Stearate, Microcrystalline Cellulose, Opadry Clear (contains Hydroxypropyl Methylcellulose and Polyethylene Glycol), Polyethylene Glycol, Povidone, Sodium Lauryl Sulfate, and Sodium Starch Glycolate.

pms-URSODIOL C comes in the following dosage forms:
Tablets: 250 mg and 500 mg

Do not use pms-UROSODIOL C if you:
- have an allergy to ursodiol or to any ingredient in the formulation.
- have a blockage of bile flow due to widespread liver disease.
- have a complete blockage of bile flow due to disease outside of the liver.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take pms-URSOIOL C. Talk about any health conditions or problems you may have, including if you:
- have taken pms-URSODIOL C before and it was not well-tolerated or caused an allergy.

- have liver problems, or are in need of a liver transplant.
- have a partial blockage of bile flow due to disease outside of the liver.
- have variceal bleeding (bleeding from swollen veins, arteries, or lymph vessels).
- have ascites (swelling in the abdomen).
- are pregnant, plan to become pregnant, are breast-feeding or plan to breast-feed.
- need other medical treatment by another healthcare professional, let him or her know that you are taking pms-URSODIOL C.

Other warnings you should know about:

Laboratory tests: Your healthcare professional may do certain tests during your treatment. These include liver function tests and bilirubin levels every month for three months after start of treatment, and every six months thereafter.

Bezoars in Patients with a Risk for Blockage in the Gut (intestine): A bezoar is where material builds up in the stomach or gut, causing a blockage. This can cause symptoms such as nausea, vomiting, and pain in the belly area. Bezoars may cause a blockage that requires surgery. This very rare side effect happened in patients who were taking ursodiol and had medical conditions that caused stomach or gut blockage (such as previous gut surgery or Crohn's disease).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with pms-URSODIOL C:

- Medicines that reduce the amount of bile acids such as cholestyramine or colestipol
- Antacids that contain aluminum
- Cyclosporine
- Dapsone
- Nitrendipine

How to take pms-URSODIOL C:

Take pms-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 healthcare professional. Follow your healthcare professional's instructions. Do not change the dose or stop the treatment without your healthcare professional's advice.

Usual dose:

Your healthcare professional would have prescribed the amount of pms-URSODIOL C you should take each day for your medical condition. pms-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.

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

If you think you, or a person you are caring for, have taken too much pms-URSODIOL C, contact a healthcare professional, 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.

What are possible side effects from using pms-URSODIOL C?
These are not all the possible side effects you may have when taking pms-URSODIOL C. If you experience any side effects not listed here, tell your healthcare professional.
Side effects include:

- Dizziness
- Headache
- Indigestion
- Itchiness
- Swelling of the extremities

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Anemia (decreased number of red blood cells): fatigue, loss of energy, looking pale, shortness of breath, weakness		✓	
Blood glucose increased		✓	
RARE			
Intestinal blockage or obstruction (blockage that stops or impairs passage of contents of intestines): cramping pain in abdomen that may begin suddenly, bloating, loss of appetite, pain that comes and goes but will then last, nausea and vomiting, constipation or diarrhea			✓

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
UNKNOWN			
Swelling beneath the skin and Swelling of the throat			✓
Palpitations: fast-beating, fluttering or pounding heart	✓		
Eosinophilia (increased numbers of certain white blood cells): abdominal pain, rash, weight loss, wheezing.		✓	
Allergic Reaction**:** difficulty swallowing or breathing, wheezing, feeling sick to your stomach and throwing up, hives or rash, swelling of the face, lips, tongue or throat.			✓
Neutropenia (decreased number of certain white blood cells): infections, fatigue, fever, aches, pains and flu-like symptoms		✓	
Interstitial lung disease: shortness of breath at rest, dry cough			✓
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		✓	
Skin Reactions: Severe inflammation and peeling of the skin, skin redness and papular skin lesions (small solid bumps on skin), or sensitivity to Light			✓
New or worsening Jaundice: yellow appearance of the skin and white portion of the eyes			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.htm) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

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

Keep out of reach and sight of children.

If you want more information about pms-URSODIOL C:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), or by contacting the sponsor Pharmascience Inc. at: 1-888-550-6060.

This leaflet was prepared by Pharmascience Inc.

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