PRODUCT MONOGRAPH

pms-URSODIOL

Ursodiol Tablets USP

250mg

LITHOLYTIC AGENT

PHARMASCIENCE INC.
6111 Royalmount Avenue, Suite 100
Montreal, Quebec H4P 2T4

DATE OF PREPARATION:
August 29, 2006

Control No. 087654

PRODUCT MONOGRAPH

pms-URSODIOL

Ursodiol Tabalets USP

250mg

THERAPEUTIC CLASSIFICATION

Litholytic agent

ACTION AND CLINICAL PHARMACOLOGY

Ursodiol, a naturally occurring bile acid, is present as a minor fraction of the total human bile acids. Oral administration of ursodiol increases this fraction in a dose related manner, to become the major biliary acid. Since in patients with gallstones, the total bile acid pool size is generally reduced, the exogenous supply of ursodiol helps to increase this bile acid pool size and increases the cholesterol saturation index. In addition, the fecal bile acid loss is increased and cholesterol secretion into the bile is reduced, without a concomitant reduction in phospholipids. Consequently, the cholesterol saturation of bile is reduced, allowing gradual solubilization of cholesterol from gallstones to occur.

Single-Dose Crossover Comparative Bioavailability Study of pms-URSODIOL 2 x 250 mg Tablets, Lot # NB070-93, Mfr. Date January 21, 2003, was performed *versus* Axcan Pharma Inc., URSO 2 x 250 mg Tablets, Lot # FN47, Exp. Date September 2004, 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** pms-URSODIOL	**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	83.30	111.71
AUC_I (ng.h/mL)	14061.8 15036.8 (34.2)	12871.9 14120.3 (37.0)	109.24	94.20	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.

INDICATIONS AND CLINICAL USE

pms-URSODIOL is indicated for the dissolution of gallstones and the treatment of associated symptoms in patients with radiolucent, noncalcified gallstones of less than 20 mm size in well opacifying gallbladders in whom cholecystectomy would be undertaken except:

– for patients who refuse surgery,
– for the presence of increased surgical risk due to systemic disease, advanced age and idiosyncratic reaction to general anesthesia.

Likelihood of therapeutic success with ursodiol is far greater if the stones are floatable or if the stone size is smaller since the dissolution rate is inversely proportional to the size of the stones. A study has shown no complete dissolution for gallstones with a diameter greater than 15mm. Safety of use of pms-URSODIOL beyond 24 months is not established.

Ursodiol is not indicated for the treatment of decompensated cirrhosis. pms-URSODIOL is not approved for the management of cholestatic liver diseases, such as primary biliary cirrhosis (PBC).

CONTRAINDICATIONS

pms-URSODIOL is contraindicated in patients:

- with known hypersensitivity to bile acids,
- with compelling reasons unremitting acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis or biliary-gastrointestinal fistula,
- with calcified cholesterol stones, radiopaque stones or radiolucent bile pigment stones,
- with chronic liver disease,
- who are hypersensitive or intolerant to ursodiol or any of the components of the formulation.
- with inflammatory diseases and other conditions of the small intestine, colon and liver which interfere with entero-hepatic circulation of bile salts.

WARNINGS

Patients should be informed of the response rate (20-40%), recurrence rate (50% after 5 years) and the underlying cholecystectomy rate (4%) seen in patients while on the treatment.

Cholecystectomy as an alternative to therapy with ursodiol should be considered as it offers the advantages of immediate and permanent stone removal but carries a high risk in some patients.

PRECAUTIONS

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

PATIENT MONITORING: Lithocholic acid, the metabolite of ursodeoxycholic acid (Ursodiol) 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 level should be monitored every month for three months after start of therapy, and after six months thereafter. Serum levels of these parameters usually decrease rapidly thus demonstrating efficacy. Treatment should be discontinued if the levels of above parameters increase.

Echogram: Recommended prior to treatment to determine the presence of gallbladder stones, and at six month intervals during the first year of treatment to monitor stone dissolution; also recommended after gallstone dissolution to monitor for possible recurrence.

Cholecystogram: Recommended prior to treatment to judge if the gallbladder is functional or not, and wether gallstones are translucent (mostly cholesterol stones) or radiopaque (calcified stones, pigment stones).

Patients should be counselled on the importance of periodic visits for liver function tests and oral radiograms or ultrasonograms for monitoring stone dissolution. They should be made aware of symptoms of gallstone complications and be warned to report immediately such symptoms to the physicians.

Patients should be instructed on ways to facilitate faithful compliance with the dosage regimen throughout the usual long-term therapy.

Colorectal surveillance: Recommended when ursodiol is administered long-term. (For details, see CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY and TOXICOLOGY Section)

Drug Interactions: Bile acid sequestrants such as cholestyramine or colestipol may interfere with the action of ursodiol by reducing its absorption. Aluminum based antacids have been shown to absorb bile acid *in vitro* and may be expected to interfere with ursodiol in the same manner as the sequestering agents.

Drugs metabolized by CYP 3A4: Studies indicate that CYP 3A4 activity may be influenced by ursodiol.

Cyclosporin: Monitoring of cyclosporin levels in ursodiol-treated patients is recommended.

Nitrendipine: Levels of nitrendipine were shown to be affected in a clinical study: 50% decrease in C_{max} and 75% decrease in AUC. It is unknown if this applied to other calcium channel blockers.

Estrogens, oral contraceptive and clofibrates: Potential increase in biliary cholesterol secretion induced by estrogens, oral contraceptive and clofibrates (and maybe other lipid-lowering drugs) may counteract the effectiveness of ursodiol.

Carcinogenesis, Mutagenesis and Impairment of Fertility: 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. Results of epidemiologic studies suggest that bile acids might be involved in the pathogenesis of human colon cancer in patients who had undergone a cholecystectomy, but direct evidence is lacking. (For details, see TOXICOLOGY Section)

Pregnancy: Teratogenic Effects: There are no adequate or well-controlled studies in pregnant women, but inadvertent exposure of 4 women to therapeutic doses of the drug in the first trimester of pregnancy during

the ursodiol trials led to no evidence of effects on the fetus or newborn baby. Reproduction studies have been performed in rats and rabbits with ursodiol doses up to 200-fold the therapeutic dose and have revealed no evidence of impaired fertility or harm to the fetus at doses of 20- to 100-fold the human dose in rats and at 5-fold the human dose (highest dose tested) in rabbits. Studies employing 100- to 200-fold the human dose in rats have shown some reduction in fertility rate and litter size. Because animal reproduction studies are not always predictive of human response, the possibility that ursodiol can cause fetal harm cannot be ruled out; hence, the drug is not recommended for use during pregnancy. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be appraised of the potential hazard to the fetus. (See also TOXICOLOGY Section)

Nursing Mothers: It is not known whether ursodiol is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ursodiol is administered to a nursing mother.
Pediatric Use: The safety and effectiveness of ursodiol in children has not been established.

Usage in Elderly: 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. As the elderly population is a sensitive population to drug-induced adverse effects, dosing should proceed with caution.

ADVERSE REACTIONS

The following adverse effects have been reported with the use of ursodiol: exacerbation of pre-existing psoriasis, rash, urticaria, dry skin, sweating, hair thinning, biliary pain, cholecystitis, constipation, stomatitis, flatulence, headache, fatigue, anxiety, depression, sleep disorder, arthralgia, myalgia, back pain, cough rhinitis.

In various clinical trials, 648 patients were treated with ursodiol. Six of 648 (1.0%) had gastrointestinal complaints: 4 had diarrhea (0.6%,) and 2, dyspepsia (0.3%). In addition, 1 patient was thought to have pruritus, 1 foot swelling and 4 other miscellaneous complaints.

SYMPTOMS AND TREATMENT OF OVER DOSAGE

Accidental or intentional overdosage of ursodiol has not been reported and likely would result only in self-limiting acute diarrhea which 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.

DOSAGE AND ADMINISTRATION

The recommended dose for pms-URSODIOL is 8 to 10 mg/kg/day which may be given in 2 divided doses, 1 tablet in the morning with breakfast and 2 to 3 tablets before bedtime with food.

Table I may be consulted to calculate the quantity of tablets to be taken per day. An incremental program of increasing dosage has not usually been employed. Dosage less than 8mg/kg/day is relatively ineffective and is not recommended.

Table I - WEIGHT DOSAGE GUIDE

Body Weight (Kg)	Recommended No. of Tablets(s)/Day
45 - 48	2
59 - 75	3
76 - 90	3
91 - 107	4
108 - 125	5

PATIENT MONITORING

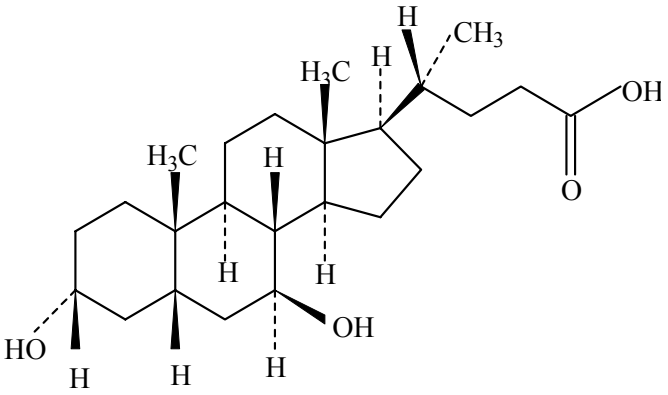
Ultrasound images of the gallbladder should be obtained at six month intervals for the first year of pms-URSODIOL therapy to monitor gallstone response. If gallstones appear to have dissolved, pms-URSODIOL therapy should be continued another 3 months and dissolution confirmed on a repeated ultrasound examination. Most patients who eventually achieve complete stone dissolution will show partial or complete dissolution at first treatment re-evaluation. If partial stone dissolution is not seen by 12 months of pms-URSODIOL therapy, the likelihood of success is greatly reduced, and therapy should be stopped.

PHARMACEUTICAL INFORMATION

Proper Name: Ursodiol

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

Structural Formula:



Molecular Formula:	$C_{24}H_{40}O_4$
Molecular Weight:	392.56 g/mol
Description:	Ursodiol is a naturally occurring bile acid. It is a bitter tasting white crystalline powder.
Solubility:	It is practically insoluble in water, freely. soluble in alcohol and glacial acetic acid; slightly soluble in chloroform and very slightly soluble in ether.
Melting Point::	200˚ - 205˚C
pKa:	6.0
pH:	Alkaline

Composition: In addition to ursodiol, as the active ingredient, pms-URSODIOL contains the following excipients (alphabetically): magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, Opadry clear (hydroxypropyl methylcellulose, polyethylene glycol), sodium starch glycolate, sodium lauryl sulfate.

STABILITY AND STORAGE RECOMMENDATIONS

pms-URSODIOL tablets should be stored at controlled room temperature, 15^{o} to 30^{o}C in a closed container.

AVAILABILITY OF DOSAGE FORMS

pms-URSODIOL is available as white, eliptical, biconvex, film-coated tablets engraved with “250" on one side and “P” logo on the other side, in strength of 250 mg in high density polyethylene bottles. Available in bottles of 100 and 500 tablets.

INFORMATION FOR THE CONSUMERS

pms-URSODIOL is ursodiol USP, a naturally occurring bile acid found in small quantities in normal human bile. pms-URSODIOL is only available by prescription. It has been prescribed for you by your physician for the dissolution of gallstones and the treatment of associated symptoms. pms-URSODIOL is used in patients who have refused surgery or in whom surgery should be avoided because of medical problems.

You should discuss with your doctor the benefit and risk of pms-URSODIOL treatment of this problem.

PLEASE READ THE FOLLOWING INSTRUCTIONS CAREFULLY IN ORDER TO GET THE FULL BENEFIT OF THIS MEDICATION

- This medication should only be used as instructed by your doctor. Comply with the terms of the prescription. 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.

- If you experience significant abdominal pain, contact your doctor.

- Before you begin using any new medicine (prescription or non-prescription) or if you develop any new medical problem while using this medicine, check with your doctor.

- Before starting treatment with this medicine pms-URSODIOL, your doctor must know:

  - if you have taken pms-URSODIOL before and if it was not well tolerated or caused an allergy,
  - if you are pregnant, or intend to become pregnant, or are breast-feeding or intend to breast-feed,
  - if you are taking other prescription and non-prescription medicines. The following products in particular have been shown to have an interaction with ursodiol: some bile acid reduction medications (such as cholestyramine or colestipol) and aluminum based antiacids. Use of these medications with pms-URSODIOL may require that the dosage of your medications be adjusted.

- Proper use of the medication: pms-URSODIOL should be taken in two divided doses with food as described on the label. It is easier to remember to take your medication, if it is taken at the same time each day. Setting a routine to take your medication helps this activity become a normal part of your day.

– Take pms-URSODIOL for the full time of treatment, even if you begin to feel better.

– If you need other medical treatment by another doctor , let him or her know that you are taking pms-URSODIOL

– Inform your doctor if you feel in any way unwell while taking pms-URSODIOL (see UNWANTED EFFECTS).

– Studies on the safety and efficacy of pms-URSODIOL in children have not been performed.

– The use of pms-URSODIOL during pregnancy must be carefully decided in discussions between you and your doctor. Should you become pregnant while taking pms-URSODIOL, discuss this immediately with your doctor.

– The use of pms-URSODIOL is not recommended while breast-feeding because of the lack of information available.

SIDE EFFECTS

In addition to its intended action, any medication may cause side effects.

These effects may appear in certain patients. They may appear and disappear without involving any particular risk but if any unwanted effect persists or becomes bothersome, you must let your doctor know about it without delay. These effects may consist of worsening of pre-existing psoriasis, rash, hives, dry skin, sweating, hair thinning, biliary pain, gall bladder inflammation, constipation, mouth inflammation, flatulence, headache, fatigue, anxiety, depression, sleep disorder, pain in a joint, muscle pain, back pain, cough, hay fever, diarrhea, indigestion and stomach cramps.

THIS MEDICATION IS PRESCRIBED FOR A PARTICULAR HEALTH PROBLEM AND FOR YOUR PERSONAL USE ONLY.DO NOT GIVE IT TO OTHER PERSON.

KEEP THIS AND ALL OTHER MEDICATION OUT OF THE REACH OF CHILDREN.
IF YOU WANT FURTHER INFORMATION, ASK YOUR DOCTOR OR PHARMACIST.

PHARMACOLOGY

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

These studies demonstrate 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 decreased cholesterol uptake in rat jejunal membrane 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. Tauroursodeoxycholicacid 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 an 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 bile. It further reduces cholesterol secretion into bile. These actions contribute to biliary cholesterol desaturation and gradual dissolution of radiolucent cholesterol gallstones by micellar solubilization.

After an oral dose (I.2 5 mg/kg) of ursodiol to mice, levels of unconjugated drug decreased rapidly in the stomach after an hour. However, levels in the small intestine (3.1 to 9.4 mg/g tissue), liver (0.2 to 0.5 mg/g tissue) and bile (4.2 to 9.1 mg/g/tissue) remained relatively constant over a sample period from five minutes to three days after administration. This is indicative of the anterohepatic recirculation of ursodiol.

In monkeys, ursodiol is conjugated with either taurine or glycine in the liver after absorption, and enters the enterohepatic circulation, whereupon it is excreted into the bile and subsequently into the intestine. In the

intestine it may be either hydrolyzed back to the free compound, or the portion which is not re-absorbed undergoes microbial conversion to lithocholic acid and is excreted in the feces.

Ursodiol is primarily excreted in the feces. Following a single oral dose of ^{14}C-ursodiol (30 mg/kg) given to rats, the cumulative percentage of radioactivity excreted in the feces was 23%, 68%, and 95% after 1, 3 and 7 days respectively, with only a trace amount found in the urine. The same dose in monkeys resulted in 75 to 95% excretion of radioactivity in the feces within 10 days.

The biological half life of exogenously administered ursodiol has been estimated to be 2.5 and 3.5 days in mice following oral and intravenous administration respectively, 2 days in Rhesus monkeys after oral dosing and 3.5 to 5.8 days in man following oral administration.

CLINICAL PHARMACOLOGY

Ursodiol (UDCA) is normally present as a minor fraction of total bile acids in humans (about 5%). Following oral administration, the majority of ursodiol is absorbed by passive diffusion and its absorption is incomplete. Once absorbed, ursodiol undergoes hepatic extraction to the extent of about 50% in the absence of liver disease. 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 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.

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. 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. Ursodiol is excreted primarily in the feces. With treatment, urinary excretion increases.

During chronic administration of ursodiol, it becomes a major biliary and plasma bile acid. At a chronic dose of 8-10 mg/kg/day, ursodiol constitutes 30-50% of biliary and plasma bile acids.

Studies in gallstone patients with normal lipid profile, have indicated that ursodiol did not affect the lipid levels. However, in patients with raised pretreatment triglyceride levels, therapy with ursodiol resulted in an overall trend towards reduction in triglyceride levels.

CLINICAL EXPERIENCE

In open studies using ursodiol, the overall dissolution rate was found to vary between 50 and 60% as compared to a rate of spontaneous dissolution of less than it. However, results varied widely between studies due to differences in dose and duration of therapy, selection criteria, rating of results and possibly diagnostic techniques used. In controlled clinical trials this rate was slightly lower (between 40-50%).

US STUDIES

Three open label studies, involving a total of 163 patients with gallstones, were conducted in the U.S.A. In these studies, either a single dose of 750 mg (two studies) or a single or divided doses of 1,000 mg/day of ursodiol were given up to 21 months.

Study Type	*Investigators*	*# of Patients*	*Dosage*	*Dissolution Rate*
1) Open	Thistle	32	3 x 250 mg b.i.d.	64%
2) Open	Salem Colatillo	62	1 x 250 mg daily 4 x 250 mg once daily or 4 x 250 mg in divided doses	56%
3) Open	Schoenfield Marks	69	3 x 250 mg once daily	39%

AVERAGE: 53%

In the study conducted by Dr. Thistle, a 64% total dissolution rate was observed after 9.6 months of treatment. Six patients were discontinued from treatment when their gallstones were noted to be calcified. None underwent cholecystectomy, but 1 was discontinued for persistent non-surgical complications of gallbladder disease, and 1 for a nonfunctional gallbladder. No serious side effects were noted. Ursodiol was well tolerated.

In the study conducted by Drs. Salem and Colalillo, a total gallstone dissolution rate of 56% was observed. 1 patient had stone recurrence. Five patients developed stone calcification and 5 others had loss of gallbladder function while on treatment. One patient had calcified stones at entry and they were unchanged after treatment. Thirteen percent of patient underwent cholecystectomy. No serious adverse effects were reported. Three patients reported 1 episode each of diarrhea while on the treatment. Mild fluctuations in liver function tests (both favourable and unfavourable) , were noted. These changes were not found to be medically significant nor a clear relationship to ursodiol was established, since all patients had preexisting gallbladder disease.

In the study conducted by Drs. Schoenfield and Marks, a total dissolution rate of 39% (22% complete, and 17% partial) was observed after 21 months of therapy with ursodiol. No effect of diet was demonstrated on total or partial dissolution rates. Ursodiol was well tolerated. Only 2 patients were discontinued due to adverse effects, 1 with hiatal hernia and complaints that ursodiol exacerbated symptoms related to that condition and the other with constipation. Also, ursodiol did not result in significant changes in laboratory parameters.

CANADIAN STUDIES

Two open label studies involving 169 patients were performed by Drs. Fisher and Williams. In both studies 10 mg/kg/day ursodiol, with or without dietary supplement, was given for up to 24 months.

In the study conducted by Dr. Fisher, a total of 111 patients were enrolled. Of these, 107 patients received ursodiol, however, most of the data were available on 100 patients. Out of these 35 patients had previously been treated with chenodiol for 1 year or more and 24 among them had not responded to the therapy.

Following therapy with ursodiol, complete (13 patients) and partial (7 patients) dissolution of gallstones was observed in 20 patients; outcome of the treatment was unknown in 35 patients as they were not re-imaged. Stone calcification occurred in 11 patients and treatment failure was noted in 7 patients. One patient had cholecystectomy and 2 patients were discontinued from the study because of gastrointestinal complaints attributed to ursodiol.

These results are not comparable with those obtained in the U.S. studies where much higher dissolution rates (up to 64%) were observed. Therefore, it must be added that the rate of dissolution is markedly influenced by patient selection.

In the study conducted by Dr. Williams 69 patients were enroled, however, 2 patients did not participate in the study. Of these 67 patients, 51 received ursodiol only and 16 were treated with ursodiol and chenadiol combination.

The true rate of dissolution was difficult to determine due to creation of sub-groups, inclusion of chenodiol therapy failure patients and patients with radio-opaque stones or non- functional gallbladders and patients with inflammatory bowel disease, and even patients who had diarrhea and no gall stones.

The dissolution rate in this study was also very low which suggests that careful selection of patients can significantly improve the anticipated dissolution rate in patient entering treatment.

In both studies ursodiol was well tolerated and no serious side effects were encountered.

EUROPEAN STUDIES

A total of 5 studies were conducted in Europe. Four of these were open labeled studies and were conducted in West Germany. The fifth study was French-Belgium cooperative study which was coordinated from Paris, France. It was a multi-center (14 centers), double-blind, randomized, comparative trial. A total of 318 patients were enrolled in all 5 studies. The dose varied from 750 mg/day to 1,250 mg/day (3-5 Tablets/day) and the duration of treatment ranged from 5 to 25 months.

The rates of gallstone dissolution varied between 37% to 64% in these studies. There were fewer than 5 different adverse effects reported in these studies. The most important were diarrhea, constipation and

infrequent mention of mild abnormalities in liver function tests. In most cases, patients remained on the study and completed the trial as scheduled.

It was, therefore, concluded that ursodiol was safe below, or at a 10 mg/kg/day dose level, this dose was well tolerated over a long period of time (2 years or more). At very low doses it was found to be less effective. At high dose (16 mg/kg/day or more), hepatotoxicity was observed in humans. At this dose, frequency and severity of diarrhea was also increased.

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 7 day observation period, did not cause any death in any of the species used. For mice and dogs, the LD_{50} was over 10 g/kg, and rats had LD_{50} , of over 5 g/kg. Hamsters were found to be more sensitive than rats and dogs as the LD for this species was calculated to be over 3.16g/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 5 weeks or alternatively at doses of 0. 0625 to 0.5 g/kg daily for 5 weeks by the intraperitoneal route.

No deaths occurred in the study with oral administration of ursodiol whereas 1 male and 1 female rat died in the 0.25 g/kg group and six males and 4 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 finding was 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.

Orally administered, ursodiol 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 1 study, ursodiol was administered orally to Sprague-Dawley rats for 26 weeks. The dosage varied between 0.1 to 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 9/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 acid orally for 26 consecutive weeks and a variety of observations were made.

The results indicated a decrease in both weight gain and an increase in water intake in 4.0 g/kg dosage group. Eight rats (4 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: Another 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 3 months. After 52 weeks, the animals were sacrificed and an autopsy was performed.

Three animals belonging to the 0.90 g/kg group; 2 in the 0.30 g/kg group and 1 in the 0.10 g/kg group died during the study. These deaths were considered to be related to ursodiol. Liver toxicity (small round-cell infiltration, vascular degeneration, necrosis of hepatic cells, phorocytosis 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, SGOT and LAP 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 STUDIES

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-Dawleyrats 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 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 STUDIES

Ursodiol was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y, $TK^{\pm}$) 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 STUDIES

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 intraperitaneal 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 dose 2.0 g/kg. Rabbits were much more sensitive than mice and rats to the toxic action of ursodiol. The administration of doses 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 reception sites, absorption and 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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