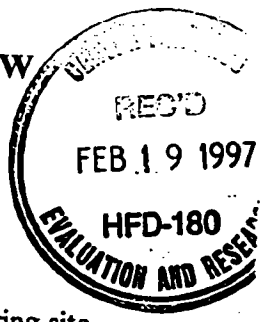
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020675

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

FEB 18 1997

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW



NDA 20-675
Ursodeoxycholic acid
Urso™ Tablets 250 mg
Axcan Pharma US Inc.

FEB 14 1997

Type of submission: Suggested bioequivalence study protocol for alternate manufacturing site.

Synopsis

The sponsors will no longer be able to manufacture Urso™ at [redacted] They have requested post-approval change in manufacturing site and manufacturing process for Urso™. The new manufacturer will be [redacted]. In a teleconference held 12/10/96 with Axcan, it was agreed that the sponsors should undertake a bioequivalence study. The sponsors were open to a suggested protocol for a bioequivalence study being sent to them for their consideration. The following protocol was discussed with Dr. Hugo Gallo-Torres, Medical Officer, HFD-180.

Recommendation:

The suggested study protocol and attached guidance should be sent to the sponsors for their consideration. The sponsors are encouraged to contact the Division of Pharmaceutical Evaluation II for clarification of any points.

[redacted] /S/ 2/13/97

Lydia C. Kaus, M.S., Ph.D.
Team Leader
Gastrointestinal and Coagulation Drug Products,
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FT initialed [redacted] /S/ 2/14/97
Mei-Ling Chen, Ph.D.
Director
Division of Pharmaceutical Evaluation II.

cc:NDA20-675, HFD-180, HFD-870(MChen, Kaus), HFD-850 (Lesko), HFD-850 (Millison), HFD-340(Viswanathan)

Protocol:
Bioequivalence study of Urso™ in healthy subjects.

Clinical Investigator: (to be filled in by sponsor)
Clinical Study Site: (to be filled in by sponsor)
Study dates: (to be filled in by sponsor)

Objective:
To determine the bioequivalence of two Urso™ formulations manufactured at two different sites and by different manufacturing processes.

Appropriate inclusion and exclusion criteria should be considered by the sponsors and fully described in the study protocol. In general, subjects should be healthy volunteers aged 18 to 50 years and within 10% of ideal body weight for height and build. Subjects should be screened for selection based on the exclusion and inclusion criteria. If female subjects are selected for the study, some assurance that the subject is not pregnant should be made. As always, written informed consent must be obtained from all study subjects prior to participation in the study.

Assay dates:(to be filled in by sponsor)
Assay site:(to be filled in by sponsor)
Batches used:(to be filled in by sponsor) The batches used must be manufactured under full production conditions and should ideally be at least [redacted] of the largest production batch/lot or a minimum of [redacted], whichever is the larger of the two.

Assay Methodology: The sponsor must ensure that the assay methodology used is sensitive, specific, linear, accurate and reproducible for measuring both conjugated and unconjugated ursodeoxycholic acid. Assurance must be made of the assay being specific to ursodeoxycholic acid and not to endogenous bile acids (such as chenodeoxycholic acid) or their metabolites. Also, the assay should be able to distinguish ursdeoxycholic acid from each of its individual conjugates.

Demographics:
The sponsors should describe the demographics of the study subjects:

	MEAN ± SD	RANGE
AGE (YEARS)		
WEIGHT (KG)		
HEIGHT (CM)		

METHODOLOGY:

Suggested Study design:
Double-blind, two-period, two-treatment, two sequence, single and multiple-dose crossover study. 30 healthy subjects (or sufficient to ensure adequate statistical results). The suggested number of 30 subjects is based on 30% variability in log transformed Cmax data (reference: Drug

Information Journal, 24, 315-323, 1990).
There should be a one month wash-out between each period of the study. Equal numbers of subjects should be randomly assigned to the two possible sequences. The study, prior to its start, should be approved by an institutional review board. Administration of single dose of the drug at 8 am, after an 8h overnight fast should occur on Day 1 and Day 28 of the study period. On those days, Urso ™ should be administered with 250 mL of an isotonic soft drink within 5 minutes minutes of drinking a glass of whole cow's milk. No further doses of Urso ™ are to be given on Day 1 and Day 28. Blood samples are to be taken following single dose administration on Day 1 of each study period and on the last day (Day 28) after mutiple dose administration. Multiple dosing will start on Day 2 of each study period; one 250 mg tablet will be taken with each meal and one tablet with a bedtime snack (as per the Lindor study). Meals should be standardized as much as possible with respect to day-to-day content and dosing interval. The morning dose should always be taken with a glass of isotonc soft drink after drinking a glass of whole cow's milk. Multiple dosing will continue for a further twenty-seven days. On the days of blood sampling subjects should refrain from eating for about four hours post-administration of the dose.

Blood sampling:
pre-dose, 0.5, 1, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0 and 12.0 hours post-dose. The last blood sampling time point is dependent on the sensitivity of the assay, a reasonable guide is up to the time at which concentrations are 10% of the highest plasma concentration measured. All samples should be processed as appropriate for the chosen assay methodology . Stored samples should be held at an appropriate storage temperature and under suitable conditions until analysis eg. plasma samples frozen at -80 °C until analysis. Evidence of stability of samples under the storage conditions should be provided by the sponsors.

[redacted]

Biological Measurements:
ANOVA and the two one-sided tests procedure are to be used in the statistical evaluation of bioequivalence. Data are to be analyzed by non-compartmental methods (see attached guidance: Statistical procedures for bioequivalence studies using a standard two-treatment crossover design).

RESULTS:
Report arithmetic , geometric means ± SD for Cmax, $AUC_{0\text{-}12h}$, T_{max} and T_{lag} for ursodeoxycholic acid and each metabolite in plasma , after single and multiple doses.

Example of tabulated information:

	Arithmetic			Geometric		
	Mean ± SD	**CV%**	**Range**	**Mean**	**Mean+ SD**	**Mean- SD**
Trt. A						
Cmax						
AUC_{0-12h}						
T_{max}						
Trt. B						
Cmax						
AUC_{0-12h}						
T_{max}						

Two one sided tests procedure results APPEARS THIS WAY ON ORIGINAL
This should be reported for ursodeoxycholic acid and each of its metabolites.

Parameter	**90% CI (Trt. A vs. Trt. B)**	**Power of two one-sided test**
Cmax		
AUC_{0-12h}		

The sponsors should provide the results from the two one-sided tests procedure for bioequivalence in terms of actual 90% confidence intervals for each parameter compared (AUC and Cmax). Specifically these need to be given as :

90% CI: (E-t(0.95)*sk), (E+t(0.95)*sk) expressed as (L, U)

where E: ln(Test mean)- ln(Reference mean)
sk: standard error of estimate
L: lower value
U: upper value
90% CI: confidence interval
t(0.95):t-value for p=0.05, degrees of freedom from error term
Lower limit of CI = exp(L)
Upper limit of CI = exp(U)

The upper and lower limits are often expressed in terms of percentages. The acceptable 90% CI

range is 80 to 125% for log transformed data.

The multiple dose part of the study should be continued until steady-state has been reached. A total dosing period of 28 days has been suggested for each arm of the study, but the sponsors may have evidence that steady state is achieved sooner. The washout period of one month is a suggested washout period to ensure that the body system returns to baseline, the sponsors may have evidence that this washout period can be shortened. The suggested liquid breakfast for the first dose is to allow dissolution to begin immediately and to give a reasonable stimulus for bile flow.

Other information that can be collected but is not necessary for showing bioequivalence:
From a scientific perspective the sponsors could obtain the following information during this study:

1. Serum lithocholic acid levels (both sulfated and nonsulfated).
2. Protein binding in normals (both albumin and lipoproteins) in order to have reference values for comparison to patient population

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

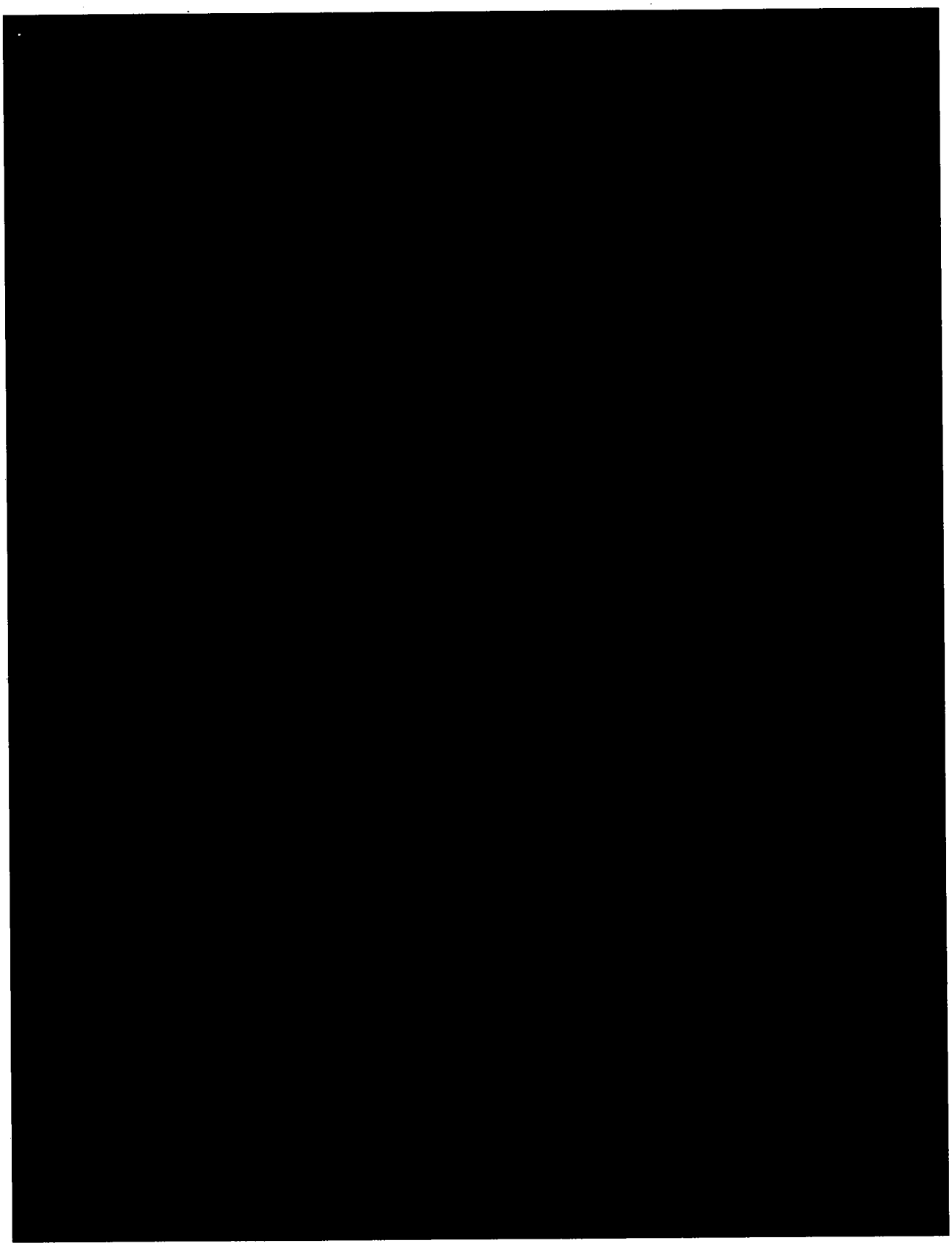
NDA 20-675 Submission Dates: June 27th, 1997.
Ursodeoxycholic acid
Urso™ Tablets 250 mg
Axcan Pharma US Inc.

AUG - 6 1997

Type of submission: Orphan Drug Status: 5, 6 P

Backgound:
The sponsor has submitted revised labeling to the FDA proposed labeling.

[redacted]



[redacted]

/S/ [redacted]

Lydia C. Kaus, M.S., Ph.D.
Team Leader, Gastrointestinal and Coagulation Drug Products, Division of Pharmaceutical Evaluation II.

cc:NDA 20-675, HFD-180, HFD-870 (Chen, Kaus), HFD-850 (Lesko), Central Document Room (Barbara Murphy)

[redacted]
APPEARS THIS WAY ON ORIGINAL

DEC 1 1 1996

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

NDA 20-675
Ursodeoxycholic acid
Urso™ Tablets 250 mg
Axcan Pharma US Inc.

Submission Dates: March 22, 1996
May 23, 1996,August 12,1996
August 23, 1996, September 18, 1996
September 27,1996.
Original Received by DPEII:April 8,1996.

Type of submission: Orphan Drug Status: 5, 6 P

Synopsis:

The proposed recommended dose for PBC is 13 to 15 mg/Kg/day administered in four divided doses with meals. The recommended adult dosing regimen is dependent on the total number of tablets being taken per day:

4 tablets/day	1 tablet with each meal and 1 tablet with a bedtime snack or as directed
5 tablets/day	1 tablets with each meal and 2 tablets with a bedtime snack or as directed
6 tablets/day	2 tablets with breakfast and a bedtime snack and 1 tablet with lunch and supper or as directed
7 tablets/day	2 tablets with breakfast, 1 at lunch, two with dinner, and 2 with a bedtime snack

The pivotal clinical trial (Lindor, Mayo) used a dosing regimen of 13 to 15 mg/Kg/day in four divided doses with meals. Two formulations were used for the 250 mg tablets in this clinical trial: one formulation was manufactured by [redacted] and one by [redacted] The [redacted] formulation used in the Mayo study will be referred to as [redacted] 1 formulation in this review. Axcan has now reverted to the [redacted] formulation that is being manufactured by the same method but by [redacted]. This is referred to as [redacted] 2 formulation in this review.

A second clinical trial (Heathcote, Canada) used a dosing regimen of 14 mg/Kg/day as a single oral dose in the evening. This trial used a 250 mg capsule formulation produced by [redacted] The Heathcote trial is considered supportive. The sponsors have an ongoing dose-response study in which three dosage regimens are being considered: 5-7 mg/Kg/day, 13-15 mg/Kg/day and 23-25 mg/Kg/day.

The sponsors undertook a literature search and it is these published articles that form the basis of the labeling. The sponsors also submitted a limited bioequivalence study with an assay that was not validated.

Recommendations:
1. It is recommended that the sponsors carry out a pharmacokinetic and pharmacodynamic study in patients with stable liver disease to characterize the distribution and elimination of ursodiol and its conjugates (measured separately) using different dosing regimens. Collection of serum, bile, urine and fecal data would enhance the knowledge concerning its pharmacokinetics and enable the determination of a suitable dosing regimen. The Division of Pharmaceutical Evaluation II can be consulted concerning the design of the study.

2. It is recommended the sponsors carry out in vitro binding studies using blood collected from patients in different stages of liver disease. The sponsors need to characterize the comparative binding of ursodiol to serum lipoproteins and albumin in the presence of its glycine and taurine conjugates and in the presence of other bile acids. Detailed information on the binding kinetics of ursodiol would determine the role of albumin and lipoproteins as carriers of ursodiol and the degree of competition of other bile acids and bilirubin on its binding.

3. It is recommended that the sponsors carry out a dose proportionality study in patients with stable liver disease to further characterize the pharmacokinetics of ursodeoxycholic acid and its conjugates.

The design of these studies would also involve active input from the Medical Division.

Comments:
1. Note that the availability of a sensitive and specific analytical techniques has increased over the last few years, enabling characterization of the pharmacokinetics of drugs and their metabolites that may be present at low concentrations in the blood.

2. Note the labeling comments on page 14 of this review.

3. The dissolution specification proposed by the sponsors is acceptable (as described on page 41 of the review).

/S/ [redacted] 12/12/96
11/5/96

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/S/ [redacted] 2/10/96

FT initialed by
Mei-Ling Chen, Ph.D.
Director, DPEII
cc:NDA 09-218, HFD-180, HFD-870(MChen, Kaus), HFD-850 (Lesko), HFD-850 (Chron, Bott, Reviewer), HFD-340(Viswanathan)

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APPENDIX II

Dissolution data

ABBREVIATIONS:

AUC.....area under the plasma concentration versus time profile
CLs.....clearance
Cmax.....maximum plasma concentration
Clcr.....creatinine clearance
CA.....cholic acid (3α,7α,12α-trihydroxy-5β-cholan-24-oic acid), bile acid
CDA=CDCA=CDC....chenodeoxycholic acid (3α,7α-dihydroxy-5β-cholan-24-oic acid), 1° bile acid
CMC.....critical micelle concentration
DCA.....deoxycholic acid (3α,12α-dihydroxy-5β-cholan-24-oic acid), 2° bile acid
LCA (LC).....lithocolic acid (3α-hydroxy-5β-cholan-24-oic acid), 2° bile acid
PBC.....primary biliary cirrhosis
PSC.....primary scelorsing cholangitis
SD.....standard deviation
SS.....steady-state
SA.....(body) surface area
tmax.....time when Cmax observed
UDCA.....ursodeoxycholic acid (3α,7β-dihydroxy-5β-cholan-24-oic acid), 3° bile acid
Vd.....volume of distribution
1°.....primary
2°.....secondary
3°.....tertiary

BACKGROUND

Ursodeoxycholic acid (UDCA) is intended for the treatment of primary biliary cirrhosis (PBC). PBC is a chronic, progressive disease of the liver. It primarily affects women (9:1 ratio females to males) and its cause is unknown. The main clinical symptoms are cholestasis, pruritus, fatigue, jaundice, hypercholesterolemia, xanthomas, variceal hemorrhage and osteomalacia. In its terminal stages, there is hyperbilirubinemia (>100 μmol/L), a decrease in the number of intrahepatic bile ducts and extensive fibrosis and/or cirrhosis. End-stage patients undergo orthoptic liver transplants that results in 80% of these patients surviving two years. The etiology of PBC is hypothesized to be a three-step process where first there is immunological damage to the bile duct, followed by reduced bile flow (cholestasis) with accumulation of compounds such as cytotoxins and finally, the continuing injury to the bile duct from the cytotoxins with the development of fibrosis and cirrhosis.
Currently, ursodeoxycholic acid is present on the market as a capsule (Actigall™ 300mg) and is indicated for the treatment of radiolucent gallbladder stones.

Mechanism of Action of UDCA

UDCA is possibly an immunomodulator. UDCA reduces the aberrant expression of class I human leukocyte antigens (HLA 1) on hepatocytes. UDCA may improve abnormalities in concentrations of circulating IgM, interferon γ, and activated lymphocytes. Modulation of the production of cytokines interleukin 2, 4 and γ from human mononuclear cells *in vitro* by UDCA has been noted. Since the immune pathogenesis of PBC is not fully understood, the role of UDCA in correcting the immune abnormalities is limited. UDCA increases hepatic bile excretion, which is defective in PBC patients. UDCA also competes with endogenous bile acids for reabsorption in the ileum. With UDCA treatment there is a shift in the bile acid composition from predominantly hydrophobic bile acids (more damaging to cells) to hydrophilic bile acids such as UDCA. This concept is still under debate. Lastly, UDCA may have a direct cytoprotective effect. Addition *in vitro* of UDCA to hepatocytes incubated with chenodeoxycholic acid, reduced the leakage of enzymes from cells that could be damaged by chenodeoxycholic acid.

Rationale for Selection of Starting Dose and Treatment Regimen:

The rationale for treatment is the hypothesis that long-term administration of UDCA would result in changes in the endogenous bile acid pool reducing biliary obstruction and reduction of the subsequent cholestasis and hepatocellular damage. The dosing regimen was the one used in the pivotal Mayo clinical trial.

SUMMARY OF BIOAVAILABILITY/PHARMACOKINETIC/PHARMACODYNAMICS:

Since the submission is mainly a collection of published journal articles, this review covers ADME under appropriate subheadings with reference to individual papers. Many pharmacokinetic related papers were retrieved from a MEDLINE search undertaken by the reviewer. It must be kept in mind that many studies have not measured the parent compound so that sometimes the plasma measurements of UDCA might reflect a total concentration of a number of moieties or conjugates rather than a specific moiety. UDCA is converted *in vivo* to CDA , therefore the properties of CDA have been described in the review, where appropriate.

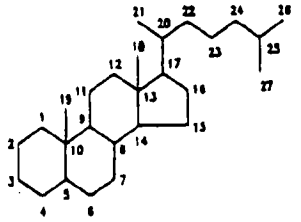


Fig. 1. Numbering system for carbon atoms of bile acid skeleton. C_{24} bile acids are termed cholanoic acids; C_{27} bile acids are termed cholestanoic acids.

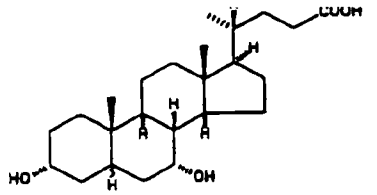


Fig. 2. Structural formula of chenodeoxycholic acid showing positions and orientation of the 3α- and 7α- hydroxy groups. The stereochemistry of the A/B ring juncture is shown by a wavy line to indicate that a bile acid is either 5β (A/B ring juncture is *cis*) or 5α (A/B ring juncture is *trans*). In semi-systematic bile acid nomenclature, 5α bile acids are termed *allo* bile acids. The figure also shows the stereochemistry of the B/C and C/D ring junctures, as well as that of the side chain with its C_{21} methyl group.

UDCA is the 7β-hydroxy epimer of CDCA. The M.Wt of UDCA is 392.56G.

I. BIOAVAILABILITY

Physicochemical properties[1]:

- UDCA is a dihydroxy bile acid.
  Aqueous solubility of protonated form for UDCA is 9μmol/L and for CDA is 27μmol/L.

- UDCA like other bile acids is amphipathic, forming micelles. CMC in 0.15 M Na^+ (physiologic concentration in body fluids) for UDCA is 7mM, and the glycine or taurine conjugates of UDCA (aminoacyl amidates) have a slightly lower CMC than UDCA. CDA has a lower CMC of 3 mM in 0.15 M Na^+ compared to UDCA.

- pK_a of UDCA is 5.1, for the glycine conjugate it is 3.9 and for the taurine conjugate it is <2.
  CMpH for UDCA is about pH 8. This is the pH where solubility increases steeply since the concentration of UDCA has reached the CMC, micelles have formed, and the concentration of dissolved molecules increases stoichiometrically with additional UDCA added to the system over a constant pH. CMpH for UDCA's glycine conjugate is

about pH 6 and for its taurine conjugate it is much lower. The CMpH for CDCA is pH 6.7.

Comment:
The CMC is important information when considering the solubilizing properties of bile acids.

- Log Partition Coefficient (n-octanol/water) for the protonated form of UDCA is 3.0 and for CDA is 3.3 . The shake-flask procedure was used to determine the log partition coefficient. Concentrations used were below the CMC for the bile acids studied[2].

PHARMACOKINETICS

Protein Binding

The major bile acid carrier is albumin, but there is also some binding to lipoproteins. Determination of protein binding was undertaken by equilibrium dialysis [3] using phosphate buffer 0.1M, pH7.2 and bovine serum albumin at 3 g/dL concentration. Bile acid was present at "tracer concentrations": this was around 10 μM/L for UDCA. 91% ±5 of UDCA was bound to bovine serum albumin. In a study on comparative binding[4], LC, its taurine conjugate (TLC) and glycine conjugate (GLC), CDC and CA were investigated. Equilibrium dialysis was used to assess binding to plasma lipoprotein and albumin. The sodium salt of each bile acid was studied at concentrations 0.05 to 150 μM for LCA, and 0.1 to 2400 μM for CDC and CA. CDC was greater than 95% bound to albumin. UDCA was not studied. In another publication[5], UDCA was found to be 76.4 % ± 7.7 bound to "plasma fraction" compared to 96.2 %±8.3 for CDA. Binding was determined by equilibrium dialysis using pooled plasma collected from healthy subjects. 0.1 mM bile acid was incubated with plasma: the plasma is reported as containing 4g% protein, but not specifically albumin. K_{aff} value for UDCA was found to be 3.8×10^4 $dm^3.mole\text{-}1$.[2]

Lipoprotein Binding

Binding to lipoproteins occurs with bile acids. The following % binding was found for UDCA and CDA[4] in fasting blood samples from healthy subjects:

	VLDL	LDL	HDL	d>1.21G/mL (lipoprotein free fraction)
CDA	16.2 ±1.7	21.7 ±3.7	50.2 ±5.1	94.6 ±9.1
UDCA	10.8 ±1.0	16.1±1.7	27.6±3.1	71.7±6.2

Comments:
Bile acids when protonated distribute into 1-octanol, but also the ionized form can

partition into 1-octanol in substantial amounts. The distribution coefficient shows an inflection point when plotted against pH, occurring at the pKa of the bile acid. The order of lipophilicity for the bile acid series is related to the number of hydroxy groups in the steroid nucleus. However, the steroid nucleus influences the overall lipophilicity. Lipoproteins can be an alternative way of bile acids being distributed in the body.

Absorption

(See also under metabolism).

Serum bile acids are the result of spillover of bile acids from the enterohepatic into the systemic circulation. Different bile acids differ in their intestinal absorption and hepatic uptake. The availability of UDCA is dependent on two things: the extent of absorption and the extent of clearance by the liver. UDCA undergoes passive absorption in the proximal small intestine. Information from patients with ileal resection with normal liver tests and serum cholesterol values, showed that when UDCA was given at a dose of 500 mg, 59% (± 8% SEM) was excreted within 24 hours from ileostomies. This suggests that there is poor absorption from the small intestine and that the colon is also involved in the absorption of UDCA[6]. Peak ileal excretion occurred in the collection period of 2 to 8 hours post-administration of UDCA. Below pH 8.0, UDCA is poorly soluble in water. The pH recorded in the ileal samples was below pH 8.0, therefore absorption of UDCA seems to rely upon solubilization by CA and CDA. The study also showed that the amidation (to taurine and glycine conjugates) of UDCA in the ileal samples increased with time, occurring mainly 4 hours post-administration of UDCA.

In a study using healthy volunteers (four males and three females), 500 mg of ^{14}C-UDCA was administered after an 18 hour fast. Total UDCA measured (ie radiolabelled UDCA or UDCA after enzymatic deconjugation), was detected in the plasma within 40 minutes post-administration and reached a peak between 60 to 80 minutes. Plasma levels were measured up to 240 minutes. A second peak may be observed around 180 minutes. In a second group of healthy volunteers in the same study, jejunal samples were taken by means of intubation and aspiration. The jejunal samples showed both solubilized and solid particles of UDCA and 86 to 97% of the radioactive bile acids extracted were unconjugated UDCA. The amount of conjugated UDCA and the time of its appearance in the jejunal samples varied from being undetected for the duration of the study to being detected after 200 minutes. The secondary peaks could be due to intestinal absorption at two different sites (jejunal and ileal absorptions), small intestinal absorption followed by enterohepatic re-circulation of UDCA or erratic gastric emptying[7].

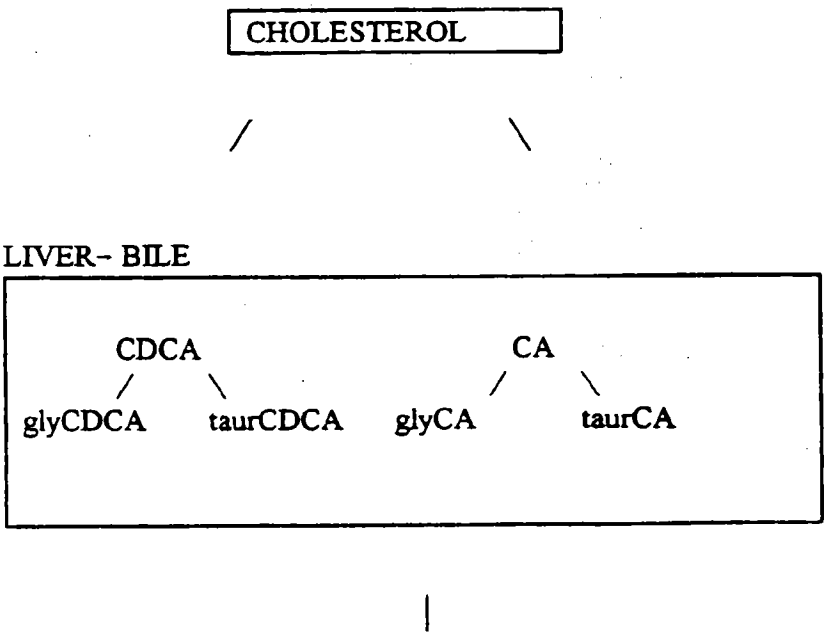
In a further study by Stiehl et al., patients with ileostomies showed increased ileal excretion of CA and CDA following administration of one dose of UDCA, but when CDA was administered, CA showed no increase in comparison to CDA ileal excretion[8]. This may suggest competition in the intestinal absorption of primary bile acids by UDCA.

A recent pharmacokinetic study by Roda et al. in 1994, looked at an enteric coated formulation of the sodium salt of UDCA[9]. Six healthy subjects received the following treatments in a randomized order and separated by a ten-day washout period:
Trt 1- 450 mg UDCA in a gelatin capsule
Trt 2- 475 mg sodium salt UDCA in a [redacted]
Trt 3- 475 mg of [redacted] sodium salt UDCA
Trt 4- 515 mg of glycoursodeoxycholic acid in a [redacted]
Trt 5- 540 mg of [redacted] sodium salt of glycoursodeoxycholic acid
An assay specific for UDCA was used. All treatments were taken after a standard meal.
The first peak occurred after 1 hour and a second peak was observed in the plasma after four hours post-administration of UDCA (trt 1). The intersubject variability was high for Cmax. Trt 2 gave comparative plasma-time profiles to trt 1. Trt 3 showed almost no UDCA levels for 2 hours and then reached a Cmax at about 3 to 4 hours. Cmax was on average about four times higher after trt3 than either trt 1 or 2 and was highly variable. The mean AUC was higher after trt 3 than the other treatments.

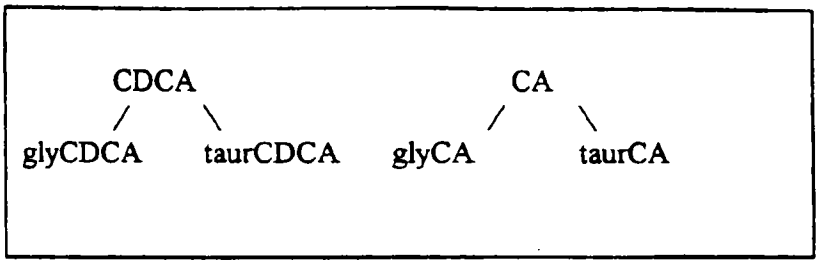
METABOLISM AND EXCRETION[1]

Primary bile acids are CDA and CA.

Bile acid metabolism:



INTESTINE



In the liver, UDCA and the main bile acids, are conjugated with taurine or glycine to become part of the enterohepatic cycle. Conjugated bile acids are secreted into the bile from which they are excreted into the intestine.

JEJUNUM:

- glyCDCA and glyCA are passively absorbed. Glycine and taurine conjugates of DCA are also passively absorbed.

ILEUM:

- glycine and taurine conjugates of CDCA and CA undergo active absorption. UDCA is actively absorbed and competes with endogenous bile acid conjugates for absorption. Some deconjugation of UDCA by the gut bacteria occurs in the ileum.

- Some deconjugation to CDCA and CA occurs. There is active absorption of the unconjugated bile acids and re-conjugation in the liver.

COLON:

- 7-αdehydroxylation is mediated by anaerobic bacteria: CA is converted to DCA and CDCA is converted to LCA. 20 to 50% of DCA is passively absorbed to be conjugated with glycine or taurine in the liver and then secreted in the bile. Less absorption of LCA occurs. LCA returns to liver where it is conjugated to glycine, taurine and a fraction of these are sulfated at the 3 position. Sulphated glycine and taurine conjugates of LCA are rapidly excreted in the feces. Some UDCA is 7-dehydroxylated to LCA.

UDCA

There is very little endogenous UDCA (7-β-hydroxy epimer of CDA) in the body[10] being less than 5% of bile acids in healthy volunteers. It is likely that UDCA is formed by bacterial epimerization of 7-hydroxy group of CDCA: this is still under debate. Then UDCA is absorbed passively in the small intestine.

After dosing with UDCA, UDCA-glycine and taurine are both actively and passively

absorbed from the small intestine

Biliary Bile acid Composition:
PBC patients before and after treatment with UDCA[11]:

	Before Treatment with UDCA	After Treatment with UDCA 300 mg bid with food
	% Molar (Mean±sem)	% Molar (Mean±sem)
CDA	31.4±1.7	21.3±1.8
CA	47.3±3.5	35.4±2.6
DCA	16.8±3.2	6.6±1.5
LCA	2.9±0.1	2.8±0.9
UDCA	1.6±1.0	34.0±1.3

PBC patients and control group before and after treatment with UDCA[12]batt93 showing mean±SD:

	Patients			Control|| (healthy subjects)	
	Before UDCA	After UDCA	Placebo	Before UDCA	After UDCA
	% Molar	% Molar	% Molar	% Molar	% Molar
CDA	33 ±8	29±8	41±2	24±5	18±3
CA	62±8	33±9	57±2	49±8	15±2
DCA	3±3	5±3	0.4±0.2	25±6	9±0.3
LCA	0.7±0.3	1±1	0.5±0.2	1±1	2±0.4
UDCA	0.3±0.2	31±12	0.1±0.1	1±1	55±7
Others**	1±0.2	1±1	1±0.4	-	1±0.2

**1β,3α,12α-trihydroxy-5β-cholanoic acid. 1β,3α,7β-trihydroxy-5β-cholanoic acid, 1β,3α,7α,12α-tetrahydroxy-5β-cholanoic acid. Iso-ursodeoxy cholic acid, ursocholic acid, hyocholic acid, ω-muricholic acid.
Bile acids were quantified by capillary gas-liquid chromatography.
||Bile acid was obtained from four healthy subjects. Ursodiol (900 mg/day) was fed for 10 days, and bile was collected before and on the last day of bile acid feeding.

Patients were given 900 mg/day (or 10-12mg/Kg/day) of ursodeoxycholic acid (Ursodiol) in the form of capsules. Note that no indication was made in this publication whether the dose was divided or given as a single dose.

As for the composition of bile acid, it can be seen that the % CDA out of the total bile acid pool remains the same, irrespective of treatment with UDCA. The % CA shows differences between studies in that there may be a decrease or its % contribution remains the same. DCA is present in healthy subjects in comparison to CA and there is a decrease in its % contribution with UDCA treatment. The consistent change can be seen in the % UDCA, irrespective of the disease state, i.e. there are marginal levels pre-treatment and then substantial increase post-treatment[9] (see also serum levels of bile acids under Section VI). In terms of the presence of conjugated vs. unconjugated bile acid, about 6% unconjugated bile acids can be found in the bile. CA predominates. In healthy subjects (control), this % is much lower being about 0.5%. UDCA treatment results in UCDA becoming the predominant bile acid and a decrease in other free bile acids.

Hepatic enzymes preferentially conjugate bile acids with taurine in disease states where there are reduced synthesis rates of endogenous bile acids. When bile acid synthesis is normal (300-500 mg/day), conjugation increases and since the availability of glycine is very much larger, glycine conjugation predominates. UDCA treatment results in increased glycine conjugation with depletion of taurine for conjugation. In patients with cholestatic disease there are also some minor paths of metabolism eg hydroxylation of 1 or 6 positions[1].

Turnover and First-Pass Metabolism

With miscalculations in published journal articles and lack of measuring the bile vs. total bile acid, turnover rates etc. cannot be substantiated. The extraction ratio for UDCA was 0.53 ± 0.01 (SEM) in patients without liver disease and was 0.43 ± 0.05 (SEM) in mild and 0.07 ± 0.01 (SEM) in severe liver disease.[13] Note that a nonspecific assay was used.

Fecal Bile acid composition

In a study in which three patients (cholelithiasis and/or hyperlipidemia) were followed after feeding with 1 G/day UDCA and 1 G/day of CDA on separate occasions, the fecal bile acid composition was:

Fecal bile acid composition during UDCA and CDA administration (Mean % ± SD)[10]

Trt	LCA	DCA	CDA	UDCA	CA	7-keto-LCA
UDCA	44.3±19.1	16.7±8.5	9.0±5.2	15.0±15.6	8.3±10.1	6.7±3.8
CDA	69.0±7.0	11.3±6.0	18.7±1.2	0	1.1±1.0	trace

UDCA is measured as total amount; there was no distinction between free and conjugated UDCA.

In a study in healthy subjects given 500 mg of ^{14}C-UDCA, fecal samples collected for 72 hours, showed a mean excretion of 28% of the administered dose. Further analysis using TLC showed that the radioactivity was in the form of free bile acids, the major one being LA (31% of the 28% recovered in the feces)[7]. Since urinary excretion of UDCA is low in healthy subjects in particular, the fecal collection might have been incomplete.

Treatment	Bile Acids (μM/G creatinine)				
	Uncommon			Others§	Total
	Endogenous†	Hydroxylated‡	Ursodiol		
Patients					
Pretreatment‖	37.3 ± 16.7	14.2 ± 10.2	2.9 ± 0.5	7.8 ± 2.8	62.2 ± 22.2
Placebo¶	35.7 ± 14.7	12.4 ± 8.9	2.7 ± 0.6	8.1 ± 2.4	58.9 ± 18.6
Ursodiol** (6 mo)	23.5 ± 8.7††	13.7 ± 5.4	77.9 ± 19.7‡‡	23.9 ± 7.8	139.0 ± 28.9‡‡
Ursodiol** (12 mo)	24.9 ± 7.8††	15.0 ± 4.8	120.1 ± 33.6‡‡	38.6 ± 12.7	198.6 ± 42.7‡‡
Ursodiol** (24 mo)	18.5 ± 4.5††	11.5 ± 4.7	96.9 ± 23.9‡‡	35.0 ± 8.7	161.9 ± 34.7‡‡
Controls§§					
Pretreatment	1.7 ± 0.3		0.3 ± 0.1	0.5 ± 0.1	2.5 ± 0.4
Ursodiol (2 wk)	2.5 ± 0.5	2.1 ± 0.3	33.0 ± 6.7	11.1 ± 2.2	48.7 ± 7.3

* Urinary bile acids were quantified by capillary gas-liquid chromatography. Values are reported as percentage of total bile acids.
† Chenodeoxycholic acid, cholic acid, deoxycholic acid, lithocholic acid.

Renal Elimination

Urinary bile acids are about fifty times higher in patients compared to healthy subjects. Normally, there is little bile acid excretion into the urine. CA is the major bile acid found in the urine of patients. Also, 1- and 6-hydroxylated CDA and CA derivatives can be found. With UDCA treatment, UDCA predominates as the bile acid excreted, doubling to tripling the amount of total bile acid being excreted[12].

Effect of UDCA treatment on urinary bile acids in patients with PBC:

In a study in healthy subjects given 500 mg of ^{14}C-UDCA, urinary elimination of UDCA was measured in four subjects over 24 hours. Less than 0.01% of the initial dose was detected; no distinction was made between free and other metabolites of UDCA [7].

Dose proportionality
There have been no appropriate dose proportionality studies carried out.

IV. SPECIAL POPULATIONS

Renal Disease
Not addressed by the sponsors.

Gender
The disease PBC primarily affects middle-aged women. The clinical studies reflect this population.

Elderly
This was not addressed by the sponsors.

Race
The sponsor did not address the effect of race on the disposition of ursodeoxycholic acid.

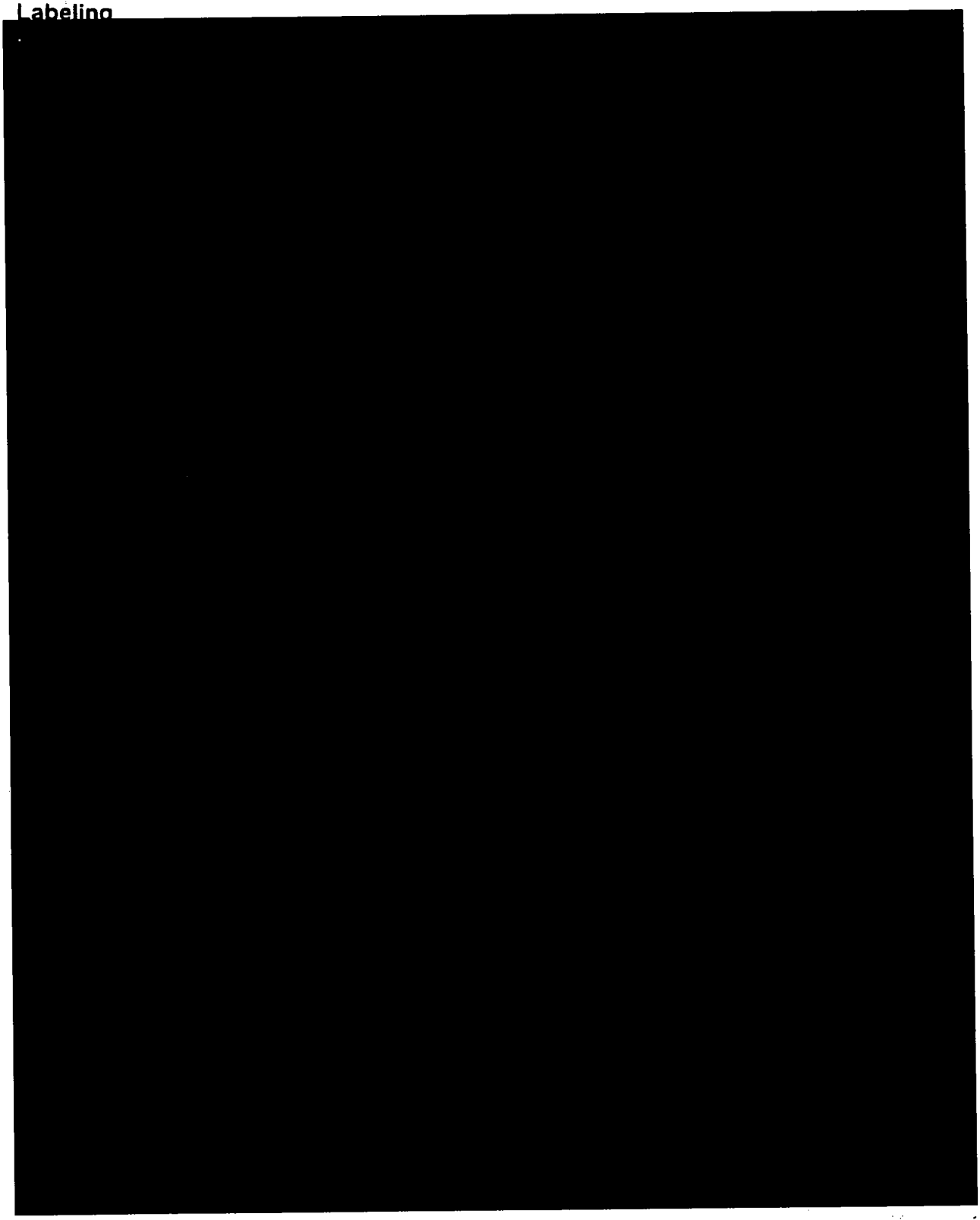
V. DRUG INTERACTIONS

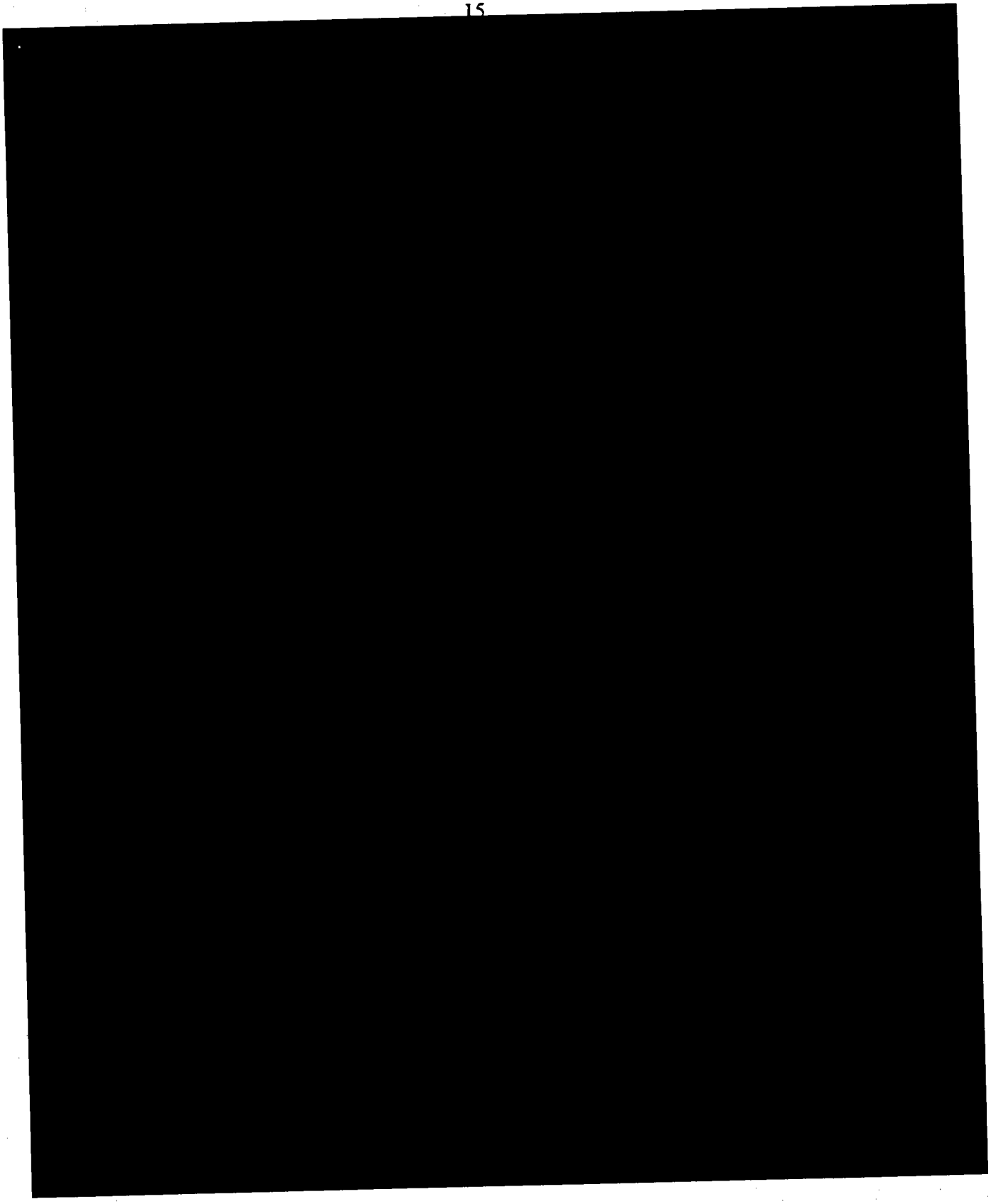
No drug interaction studies were undertaken by the sponsors.

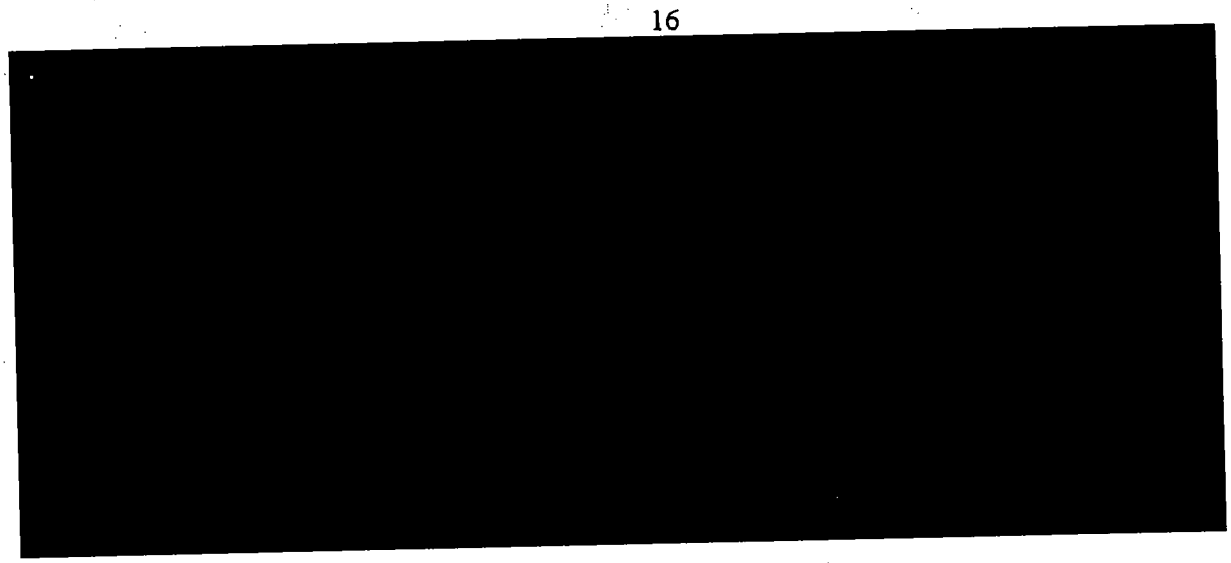
VI. PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS

Fasting serum levels of bile acids in patients with moderate to severe PBC show increased concentrations. CDA is the primary bile acid found in serum of healthy subjects (controls). Little LCA nor DCA is found in the serum (these are the 7α-dehydroxylation products of CDA and CA respectively). CDA and CA decrease in the serum with UDCA treatment. In the bile acid pool, there is a rise in the molar % of UDCA with a decrease in molar % of CA. There are contradictory observations on the change in molar % of CDA in bile after UDCA treatment. Clinical trials in PBC have focussed on reduction of serum bilirubin and liver enzymes in assessing the effect of UDCA therapy. The effect of UDCA has also been addressed by using dynamic liver function tests. All these tests are to observe long term improvement in liver function and penultimately, improved survival. The liver function tests are surrogates for assessing efficacy.

Labeling







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