CENTER FOR DRUG EVALUATION AND RESEARCH

75-592

APPLICATION NUMBER:

APPROVAL LETTER

ANDA 75-592

MAY 25 2000

Copley Pharmaceutical, Inc.
Attention: Vincent Andolina
25 John Road
Canton, MA 02021

Dear Sir:

This is in reference to your abbreviated new drug application dated February 23, 1999, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Ursodiol Capsules USP, 300 mg.

Reference is also made to your amendments dated April 9, and September 28, 1999; and April 27, 2000.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Ursodiol Capsules USP, 300 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Actigall Capsules, 300 mg, of Novartis Pharmaceuticals Corporation). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy that you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug

Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

Gary Buehler
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

75-592

APPLICATION NUMBER:

APPROVED DRAFT LABELING

Ursodiol Capsules, USP

508101
LEA508101 ℞ Only
Revised: September 1999

Prescribing Information

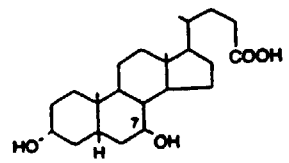
SPECIAL NOTE

Gallbladder stone dissolution with ursodiol treatment requires months of therapy. Complete dissolution does not occur in all patients and recurrence of stones within 5 years has been observed in up to 50% of patients who do dissolve their stones on bile acid therapy. Patients should be carefully selected for therapy with ursodiol, and alternative therapies should be considered.

DESCRIPTION

Ursodiol is a bile acid available as 300-mg capsules suitable for oral administration.

Ursodiol is ursodiol USP (ursodeoxycholic acid), a naturally occurring bile acid found in small quantities in normal human bile and in larger quantities in the biles of certain species of bears. It is a bitter-tasting, white powder freely soluble in ethanol and glacial acetic acid; slightly soluble in chloroform; sparingly soluble in ether; and practically insoluble in water. The chemical name for ursodiol is 3α,7β-Dihydroxy-5β-cholan-24-oic acid ($C_{24}H_{40}O_4$). Ursodiol USP has a molecular weight of 392.58. Its structural formula is shown below:



Inactive Ingredients. Magnesium stearate, colloidal silicon dioxide, corn starch, pharmaceutical glaze (modified) in SD-45, synthetic black iron oxide, propylene glycol, FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, and D&C Yellow No. 10 Aluminum Lake.

The capsule shell consists of gelatin, FD&C Red No. 40, and titanium dioxide.

CLINICAL PHARMACOLOGY

About 90% of a therapeutic dose of ursodiol is absorbed in the small bowel after oral administration. After absorption, ursodiol enters the portal vein and undergoes efficient extraction from portal blood by the liver (i.e., there is a large "first-pass" effect) where it is conjugated with either glycine or taurine and is then secreted into the hepatic bile ducts. Ursodiol in bile is concentrated in the gallbladder and expelled into the duodenum in gallbladder bile via the cystic and common ducts by gallbladder contractions provoked by physiologic responses to eating. Only small quantities of ursodiol appear in the systemic circulation and very small amounts are excreted into urine. The sites of the drug's therapeutic actions are in the liver, bile, and gut lumen.

Beyond conjugation, ursodiol is not altered or catabolized appreciably by the liver or intestinal mucosa. A small proportion of orally administered drug undergoes bacterial degradation with each cycle of enterohepatic circulation. Ursodiol can be both oxidized and reduced at the 7-carbon, yielding either 7-keto-lithocholic acid or lithocholic acid, respectively. Further, there is some bacterially catalyzed deconjugation of glyco- and tauro- ursodeoxycholic acid in the small bowel. Free ursodiol, 7-keto-lithocholic acid, and lithocholic acid are relatively insoluble in aqueous media and larger proportions of these compounds are lost from the distal gut into the feces. Reabsorbed free ursodiol is reconjugated by the liver. Eighty percent of lithocholic acid formed in the small bowel is excreted in the feces, but the 20% that is absorbed is sulfated at the 3-hydroxyl group in the liver to relatively insoluble lithocholyl conjugates which are excreted into bile and lost in feces. Absorbed 7-keto-lithocholic acid is stereospecifically reduced in the liver to chenodiol.

Lithocholic acid causes cholestatic liver injury and can cause death from liver failure in certain species unable to form sulfate conjugates. Lithocholic acid is formed by 7-dehydroxylation of the dihydroxy bile acids (ursodiol and chenodiol) in the gut lumen. The 7-dehydroxylation reaction appears to be alpha-specific, i.e., chenodiol is more efficiently 7-dehydroxylated than ursodiol and, for equimolar doses of ursodiol and chenodiol, levels of lithocholic acid appearing in bile are lower with the former. Man has the capacity to sulfate lithocholic acid. Although liver injury has not been associated with ursodiol therapy, a reduced capacity to sulfate may exist in some individuals, but such a deficiency has not yet been clearly demonstrated.

Pharmacodynamics

Ursodiol suppresses hepatic synthesis and secretion of cholesterol, and also inhibits intestinal absorption of cholesterol. It appears to have little inhibitory effect on synthesis and secretion into bile of endogenous bile acids, and does not appear to affect secretion of phospholipids into bile.

With repeated dosing, bile ursodeoxycholic acid concentrations reach a steady state in about 3 weeks. Although insoluble in aqueous media, cholesterol can be solubilized in at least two different ways in the presence of dihydroxy bile acids. In addition to solubilizing cholesterol in micelles, ursodiol acts by an apparently unique mechanism to cause dispersion of cholesterol as liquid crystals in aqueous media. Thus, even though administration of high doses (e.g., 15 to 18 mg/kg/day) does not result in a concentration of ursodiol higher than 60% of the total bile acid pool, ursodiol-rich bile effectively solubilizes cholesterol. The overall effect of ursodiol is to increase the concentration level at which saturation of cholesterol occurs.

The various actions of ursodiol combine to change the bile of patients with gallstones from cholesterol-precipitating to cholesterol-solubilizing, thus resulting in bile conducive to cholesterol stone dissolution.

After ursodiol dosing is stopped, the concentration of the bile acid in bile falls exponentially, declining to about 5% to 10% of its steady-state level in about 1 week.

Clinical Results

Gallstone Dissolution

On the basis of clinical trial results in a total of 868 patients with radiolucent gallstones treated in 8 studies (three in the U.S. involving 282 patients, one in the U.K. involving 130 patients, and four in Italy involving 456 patients) for periods ranging from 6 to 78 months with ursodiol doses ranging from about 5 to 20 mg/kg/day, an ursodiol dose of about 8 to 10 mg/kg/day appeared to be the best dose. With an ursodiol dose of about 10 mg/kg/day, complete stone dissolution can be anticipated in about 30% of unselected patients with uncalcified gallstones <20 mm in maximal diameter treated for up to 2 years. Patients with calcified gallstones prior to treatment, or patients who develop stone calcification or gallbladder nonvisualization on treatment, and patients with stones >20 mm in maximal diameter rarely dissolve their stones. The chance of gallstone dissolution is increased up to 50% in patients with floating or floatable stones (i.e., those with high cholesterol content), and is inversely related to stone size for those <20 mm in maximal diameter. Complete dissolution was observed in 81% of patients with stones up to 5 mm in diameter. Age, sex, weight, degree of obesity, and serum cholesterol level are not related to the chance of stone dissolution with ursodiol.

A nonvisualizing gallbladder by oral cholecystogram prior to the initiation of therapy is not a contraindication to ursodiol therapy (the group of patients with nonvisualizing gallbladders in the ursodiol studies had complete stone dissolution rates similar to the group of patients with visualizing gallbladders). However, gallbladder nonvisualization developing during ursodiol treatment predicts failure of complete stone dissolution and in such cases therapy should be discontinued.

Partial stone dissolution occurring within 6 months of beginning therapy with ursodiol appears to be associated with a >70% chance of eventual complete stone dissolution with further treatment; partial dissolution observed within 1 year of starting therapy indicates a 40% probability of complete dissolution.

Stone recurrence after dissolution with ursodiol therapy was seen within 2 years in 8/27 (30%) of patients in the U.K. studies. Of 16 patients in the U.K. study whose stones had previously dissolved on chenodiol but later recurred, 11 had complete dissolution on ursodiol. Stone recurrence has been observed in up to 50% of patients within 5 years of complete stone dissolution on ursodiol therapy. Serial ultrasonographic examinations should be obtained to monitor for recurrence of stones, bearing in mind that radiolucency of the stones should be established before another course of ursodiol is instituted. A prophylactic dose of ursodiol has not been established.

Gallstone Prevention

Two placebo-controlled, multicenter, double-blind, randomized, parallel group trials in a total of 1316 obese patients were undertaken to evaluate ursodiol in the prevention of gallstone formation in obese patients undergoing rapid weight loss. The first trial consisted of 1004 obese patients with a body mass index (BMI) ≥ 38 who underwent weight loss induced by means of a very low calorie diet for a period of 16 weeks. An intent-to-treat analysis of this trial showed that gallstone formation occurred in 23% of the placebo group, while those patients on 300, 600, or 1200 mg/day of ursodiol experienced a 6%, 3%, and 2% incidence of gallstone formation, respectively. The mean weight loss for this 16-week trial was 47 lb for the placebo group, and 47, 48, and 50 lb for the 300, 600, and 1200 mg/day ursodiol groups, respectively.

The second trial consisted of 312 obese patients (BMI ≥ 40) who underwent rapid weight loss through gastric bypass surgery. The trial drug treatment period was for 6 months following this surgery. Results of this trial showed that gallstone formation occurred in 23% of the placebo group, while those patients on 300, 600, 1200 mg/day of ursodiol experienced a 9%, 1%, and 5% incidence of gallstone formation, respectively. The mean weight loss for this 6 month trial was 64 lb for the placebo group, and 67, 74, and 72 lb for the 300, 600, and 1200 mg/day ursodiol groups, respectively.

ALTERNATIVE THERAPIES

Watchful Waiting

Watchful waiting has the advantage that no therapy may ever be required. For patients with silent or minimally symptomatic stones, the rate of development of moderate-to-severe symptoms or gallstone complications is estimated to be between 2% and 6% per year, leading to a cumulative rate of 7% to 27% in 5 years. Presumably the rate is higher for patients already having symptoms.

Cholecystectomy

For patients with symptomatic gallstones, surgery offers the advantage of immediate and permanent stone removal, but carries a high risk in some patients. About 5% of cholecystectomized patients have residual symptoms or retained common duct stones. The spectrum of surgical risk varies as a function of age and the presence of disease other than cholelithiasis.

Mortality Rates for Cholecystectomy in the U.S.
(National Halothane Study, JAMA 1966; 197:775-8)
27,600 Cholecystectomies (Smoothed Rates)
Deaths/1000 Operations***

Low Risk Patients*	Age (Yrs)	Cholecystectomy	Cholecystectomy + Common Duct Exploration
Women	0-49	.54	2.13
	50-69	2.80	10.10
Men	0-49	1.04	4.12
	50-69	5.41	19.23
High Risk Patients**			
Women	0-49	12.66	47.62
	50-69	17.24	58.82
Men	0-49	24.39	90.91
	50-69	33.33	111.11

*In good health or with moderate systemic disease.
**With severe or extreme systemic disease.
***Includes both elective and emergency surgery.

Women in good health or who have only moderate systemic disease and are under 49 years of age have the lowest surgical mortality rate (0.054); men in all categories have a surgical mortality rate twice that of women. Common duct exploration quadruples the rates in all categories. The rates rise with each decade of life and increase tenfold or more in all categories with severe or extreme systemic disease.

INDICATIONS AND USAGE

1. Ursodiol is indicated for patients with radiolucent, noncalcified gallbladder stones <20 mm in greatest diameter in whom elective cholecystectomy would be undertaken except for the presence of increased surgical risk due to systemic disease, advanced age, idiosyncratic reaction to general anesthesia, or for those patients who refuse surgery. Safety of use of ursodiol beyond 24 months is not established.
2. Ursodiol is indicated for the prevention of gallstone formation in obese patients experiencing rapid weight loss.

CONTRAINDICATIONS

1. Ursodiol will not dissolve calcified cholesterol stones, radiopaque stones, or radiolucent bile pigment stones. Hence, patients with such stones are not candidates for ursodiol therapy.
2. Patients with compelling reasons for cholecystectomy including unremitting acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis, or biliary-gastrointestinal fistula are not candidates for ursodiol therapy.
3. Allergy to bile acids.

PRECAUTIONS

Live Tests

Ursodiol therapy has not been associated with liver damage. Lithocholic acid, a naturally occurring bile acid, is known to be a lever-toxic metabolite. This bile acid is formed in the gut from ursodiol less efficiently and in smaller amounts than that seen from chenodiol. Lithocholic acid is detoxified in the liver by sulfation and, although man appears to be an efficient sulfater, it is possible that some patients may have a congenital or acquired deficiency in sulfation, thereby predisposing them to lithocholate-induced liver damage.

Abnormalities in liver enzymes have not been associated with ursodiol therapy and, in fact, ursodiol has been shown to decrease liver enzyme levels in liver disease. However, patients given ursodiol should have SGOT (AST) and SGPT (ALT) measured at the initiation of therapy and thereafter as indicated by the particular clinical circumstances.

Drug Interactions

Bile acid sequestering agents such as cholestyramine and colestipol may interfere with the action of ursodiol by reducing its absorption. Aluminum-based antacids have been shown to adsorb bile acids in vitro and may be expected to interfere with ursodiol in the same manner as the bile acid sequestering agents. Estrogens, oral contraceptives, and clofibrate (and perhaps other lipid-lowering drugs) increase hepatic cholesterol secretion, and encourage cholesterol gallstone formation and hence may counteract the effectiveness of ursodiol.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Ursodeoxycholic acid was tested in 2-year oral carcinogenicity studies in CD-1 mice and Sprague-Dawley rats at daily doses of 50, 250, and 1000 mg/kg/day. It was not tumorigenic in mice. In the rat study, it produced statistically significant dose-related increased incidences of pheochromocytomas of adrenal medulla in males (p=0.014, Peto trend test) and females (p=0.004, Peto trend test.) A 78-week rat study employing intrarectal instillation of lithocholic acid and tauro-deoxycholic acid, metabolites of ursodiol and chenodiol, has been conducted. These bile acids alone did not produce any tumors. A tumor-promoting effect of both metabolites was observed when they were co-administered with a carcinogenic agent. 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. Ursodiol is not mutagenic in the Ames test. Dietary administration of lithocholic acid to chickens is reported to cause hepatic adenomatous hyperplasia.

Pregnancy Category B

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. There have been no adequate and well-controlled studies of the use of ursodiol 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. Although it seems unlikely, the possibility that ursodiol can cause fetal harm cannot be ruled out; hence, the drug is not recommended for use during pregnancy.

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 pediatric patients have not been established.

ADVERSE REACTIONS

The nature and frequency of adverse experiences were similar across all groups.

The following tables provide comprehensive listings of the adverse experiences reported that occurred with a 5% incidence level:

Ursodiol Capsules, USP

508101

LEA508101 ℞ Only

Revised: September 1999

GALLSTONE DISSOLUTION

	Ursodiol 8 to 10 mg/kg/day (N=155)		Placebo (N=159)	
	N	(%)	N	(%)
Body as a Whole				
Allergy	8	(5.2)	7	(4.4)
Chest Pain	5	(3.2)	10	(6.3)
Fatigue	7	(4.5)	8	(5.0)
Infection Viral	30	(19.4)	41	(25.8)
Digestive System				
Abdominal Pain	67	(43.2)	70	(44.0)
Cholecystitis	8	(5.2)	7	(4.4)
Constipation	15	(9.7)	14	(8.8)
Diarrhea	42	(27.1)	34	(21.4)
Dyspepsia	26	(16.8)	18	(11.3)
Flatulence	12	(7.7)	12	(7.5)
Gastrointestinal Disorder	6	(3.9)	8	(5.0)
Nausea	22	(14.2)	27	(17.0)
Vomiting	15	(9.7)	11	(6.9)
Musculoskeletal System				
Arthralgia	12	(7.7)	24	(15.1)
Arthritis	9	(5.8)	4	(2.5)
Back Pain	11	(7.1)	18	(11.3)
Myalgia	9	(5.8)	9	(5.7)
Nervous System				
Headache	28	(18.1)	34	(21.4)
Insomnia	3	(1.9)	8	(5.0)
Respiratory System				
Bronchitis	10	(6.5)	6	(3.8)
Coughing	11	(7.1)	7	(4.4)
Pharyngitis	13	(8.4)	5	(3.1)
Rhinitis	8	(5.2)	11	(6.9)
Sinusitis	17	(11.0)	18	(11.3)
Upper Respiratory Tract Infection	24	(15.5)	21	(13.2)
Urogenital System				
Urinary Tract Infection	10	(6.5)	7	(4.4)

GALLSTONE PREVENTION

	Ursodiol 600 mg (N=322)		Placebo (N=325)	
	N	(%)	N	(%)
Body as a Whole				
Fatigue	25	(7.8)	33	(10.2)
Infection Viral	29	(9.0)	29	(8.9)
Influenza-like Symptoms	21	(6.5)	19	(5.8)
Digestive System				
Abdominal Pain	20	(6.2)	39	(12.0)
Constipation	85	(26.4)	72	(22.2)
Diarrhea	81	(25.2)	68	(20.9)
Flatulence	15	(4.7)	24	(7.4)
Nausea	56	(17.4)	43	(13.2)
Vomiting	44	(13.7)	44	(13.5)
Musculoskeletal System				
Back Pain	38	(11.8)	21	(6.5)
Musculoskeletal Pain	19	(5.9)	15	(4.6)
Nervous System				
Dizziness	53	(16.5)	42	(12.9)
Headache	80	(24.8)	78	(24.0)
Respiratory System				
Pharyngitis	10	(3.1)	19	(5.8)
Sinusitis	17	(5.3)	18	(5.5)
Upper Respiratory Tract Infection	40	(12.4)	35	(10.8)
Skin and Appendages				
Alopecia	17	(5.3)	8	(2.5)
Urogenital System				
Dysmenorrhea	18	(5.6)	19	(5.8)

OVERDOSAGE

Neither accidental nor intentional overdosing with ursodiol has been reported. Doses of ursodiol in the range of 16 to 20 mg/kg/day have been tolerated for 6 to 37 months without symptoms by 7 patients. The LD50 for ursodiol in rats is over 5000 mg/kggiven over 7 to 10 days and over 7500 mg/kg for mice. The most likely manifestation of severe overdose with ursodiol would probably be diarrhea, which should be treated symptomatically.

DOSAGE AND ADMINISTRATION

Gallstone Dissolution

The recommended dose for ursodiol treatment of radiolucent gallbladder stones is 8 to 10 mg/kg/day given in 2 or 3 divided doses.

Ultrasound images of the gallbladder should be obtained at 6-month intervals for the first year of ursodiol therapy to monitor gallstone response. If gallstones appear to have dissolved, ursodiol therapy should be continued and dissolution confirmed on a repeat ultrasound examination within 1 to 3 months. Most patients who eventually achieve complete stone dissolution will show partial or complete dissolution at the first on-treatment reevaluation. If partial stone dissolution is not seen by 12 months of ursodiol therapy, the likelihood of success is greatly reduced.

Gallstone Prevention

The recommended dosage of ursodiol for gallstone prevention in patients undergoing rapid weight loss is 600 mg/day (300 mg b.i.d.).

HOW SUPPLIED

Ursodiol Capsules USP are supplied as white opaque, body printed "Ursodiol 300 mg" with black ink, red opaque cap printed "Copley 380" with black ink.

Bottles of 100.....NDC 38245-380-10

Do not store above 86°F (30°C).

Dispense in tight container (USP).

Copley Pharmaceutical, Inc.
Canton, MA 02021

LEA508101
Revised: September 1999

NDC 38245-380-10

Ursodiol Capsules, USP

300 mg

Dispense in tight container (USP).

℞ Only

100 Capsules

Copley Pharmaceutical, Inc.
Canton, MA 02021

APPROVED MAY 25 2000

Keep this and all drugs out of the reach of children.

Do not store above 86°F (30°C).

Dosage: See package insert.

3 38245-380-10 7

LOT:
EXP:

LAB724800

NDC 38245-380-10

Ursodiol Capsules, USP

300 mg

Dispense in tight container (USP).

℞ Only

100 Capsules

Copley Pharmaceutical, Inc.
Canton, MA 02021

APPROVED MAY 25 2000

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Dosage: See package insert.

3 38245-380-10 7

LOT:
EXP:

LAB724800

NDC 38245-380-10

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300 mg

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APPROVED MAY 25 2000

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3 38245-380-10 7

LOT:
EXP:

LAB724800

NDC 38245-380-10

Ursodiol Capsules, USP

300 mg

Dispense in tight container (USP).

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100 Capsules

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Canton, MA 02021

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Dosage: See package insert.

3 38245-380-10 7

LOT:
EXP:

LAB724800

Copley Pharmaceutical Inc.
25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

April 9, 1999

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center For Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Ursodiol Capsules, USP 300 mg
ANDA # 75-592
Telephone Amendment

Dear Mr. Sporn,

Reference is made to our abbreviated new drug application for Ursodiol Capsules, USP 300 mg, submitted to the Agency on February 24, 1999 and to the telephone conversation of April 5, 1999, between O.D.G.'s Division of Bioequivalence staff member, Ms. E.Hu, Project Manager, and myself.

Ms. Hu requested a copy of the analytical methods for the free and total Ursodiol in human plasma, referenced in the Biostudy Report entitled: "Comparative, Randomized, Single-Dose, Two Way Crossover Bioavailability Study of Copley's Ursodiol Capsules, 300 mg and Novartis' Actigall® capsules, Following Administration of 600 mg Dose, Under Fasting Conditions" performed by

Accordingly, attached please find the analytical methods entitled: "A , for the Determination of Free Ursodiol in Human Plasma with , and Determination of Total Ursodiol in Human Plasma with Detection"

Please contact the undersigned at 1-781-575-7695 (FAX: 1-781-575-7362), should you have any questions or require clarification.

Thank you.

Nudelman, RAC
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH

75-592

APPLICATION NUMBER:

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 3

2. ANDA # 75-592

3. NAME AND ADDRESS OF APPLICANT
Copley Pharmaceuticals
Attn: Vincent Andolina
25 John Road
Canton, MA 02021

4. BASIS OF SUBMISSION
Reference Listed drug product: Actigall[R] by
distributed by Novartis approved in NDA #19-594.

According to patent certification, there are no active patents or periods of exclusivity in effect for the listed drug product.

The proposed drug product contains the same active ingredients and has same strength, dosages form, route of administration, indications and usage as the listed drug.

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
NA

7. NONPROPRIETARY NAME
Ursodiol, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:
Original submission: 2-23-99
Correspondence: 3-9-99 (Response to 3-5-99 T-con)
Acknowledgement: 3-16-99
FDA Deficiency Letter: 8-11-99
Amendment Response: 9-28-99
FDA Fax Deficiency: 3-28-00
Amendment Response: 4-27-00

10. PHARMACOLOGICAL CATEGORY
Gallstone Solvent

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

13. DOSAGE FORM
Solid Oral- Capsule

14. POTENCY
300 mg

15. CHEMICAL NAME AND STRUCTURE
Listed in labeling insert.

16. RECORDS AND REPORTS
N/A

17. COMMENTS
All chemistry deficiencies have been resolved satisfactorily.
Bioequivalence was found acceptable on 6/1/99 by M. Makary.
Labeling is acceptable 2/11/00 by A.Vezza.
EER is acceptable 6-23-00.

18. CONCLUSIONS AND RECOMMENDATIONS
The application is approvable.

19. REVIEWER: Karen A. Bernard, Ph.D.

DATE COMPLETED: 5-2-00

Page(s) 16

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Clem Rev 3

5/2/00

CENTER FOR DRUG EVALUATION AND RESEARCH

75-592

APPLICATION NUMBER:

BIOEQUIVALENCE

Ursodiol	Copley Pharmaceutical Inc.
300 mg capsule	Canton, Massachusetts
ANDA #75-592	Submission date:
Reviewer: Moheb H. Makary	February 23, 1999
75592SD.299	April 8, 1999

Review of an in-vivo Bioavailability Study and Dissolution Testing Data

I. Objective:

Copley Pharmaceutical Inc., has submitted an *in vivo* bioequivalence study (single-dose fasting) comparing its test product Ursodiol Capsule, 300 mg to the reference listed product, Novartis's Actigall^{R} Capsule, 300 mg. The firm also submitted comparative *in vitro* dissolution data.

II. Background

Ursodiol (ursodeoxycholic acid) is a naturally occurring bile acid found in small quantities in normal human bile and in larger quantities in the biles of certain species of bears. It is a bitter-tasting, white powder freely soluble in ethanol, and in glacial acetic acid, slightly soluble in chloroform, sparingly soluble in ether, and practically insoluble in water. Ursodiol is an agent intended for dissolution of radiolucent gallstones.

Ursodiol suppresses hepatic synthesis and secretion of cholesterol, and also inhibits intestinal absorption of cholesterol. With repeated dosing, bile ursodeoxycholic acid concentrations reach a steady state in about three weeks. Although insoluble in aqueous media, cholesterol can be solubilized in at least two different ways in the presence of dihydroxy bile acids. In addition to solubilizing cholesterol in micelles, ursodiol acts by an apparently unique mechanism to cause dispersion of cholesterol as liquid crystals in aqueous media. The overall effect of ursodiol is to increase the concentration level at which saturation of cholesterol occurs.

About 90% of a therapeutic dose of ursodiol is absorbed in the small intestine after oral administration. After absorption, ursodiol enters the portal vein and undergoes efficient extraction from portal blood by the liver where it is conjugated with either glycine or taurine and is then

secreted into the hepatic bile ducts. Ursodiol in bile is concentrated in the gallbladder and expelled into the duodenum in gallbladder bile via the cystic and common ducts by gallbladder contractions provoked by physiologic responses to eating. Most of the ursodiol expelled is reabsorbed in the small intestine and enters the portal vein. This enterohepatic circulation of ursodiol continues and small quantities of ursodiol are lost through feces and urine. Only small quantities of ursodiol appear in the systematic circulation and very small amounts are excreted into urine. A small portion of ursodiol undergoes bacterial degradation with each cycle of enterohepatic circulation.

Ursodiol can be both oxidized and reduced at the 7-carbon, yielding either 7-keto-lithocholic acid or lithocholic acid, respectively. Further, there is some bacterially catalyzed deconjugation of glyco- and tauro-ursodeoxycholic acid in the small intestine.

III. Study# 981791 For Single Dose Fasting Bioequivalence Of Copley's Ursodiol 300 mg Capsules

Clinical site:	Phoenix International Life Science Inc. Montreal, Canada
Study date:	Group I (subjects 1-32) Period I 7/8/1998 Period II 8/5/1998 Group II (subjects 33-74) Period I 7/15/1998 Period II 8/12/1998
Sample analysis:	Sample analysis began on October 27, 1998 and was completed on December 10, 1998.
Study design:	A single-dose, randomized, two-treatment, two-period, two-sequence crossover design.
Subjects:	A total of seventy-four (74) healthy adult, male subjects were entered into the study and 72 subjects completed the study. Statistical and pharmacokinetic analyses for free and total ursodiol

were performed on data from 70 subjects (Nos. 1-11, 13-18, 20-70, 72 and 74).

Selection criteria: Selection criteria listed in Vol. 1.1, page 000123.

Dose and treatment: All subjects completed an overnight fast (at least ten hours) before any of the following drug treatments:

Test Product: a) 2x300 mg Ursodiol Capsules (Copley), lot #380Z03, batch size Capsules, potency 101.3%, content uniformity 100.5% (%CV=1.0).

Reference Product: b) 2x300 mg Actigall^{R} Capsules (Novartis), lot #166899, Exp. 12/1999, potency 99.7%, content uniformity 99.4% (%CV=0.7).

Washout period: Four weeks

Food and fluid intake: Standard low fat meals were provided at 60, 48, 44, 39, 20 and 15 hours prior to dosing. In addition, a standard low fat snack was administered at 36 and 12 hours prior to dosing. Subjects fasted overnight for at least 10 hours before dosing and for 4 hours after dosing. Standard meals were provided at approximately 4 and 9 hours after drug administration. Water was not permitted for 1 hour before until 1 hour after dosing, but was allowed at all other times.

Housing: Subjects were housed from at least 48 hours before drug administration until after the 96-hour blood sample.

Blood samples: Blood samples were collected at: -24, -17, -10 hours and at 0 hour (prior to dosing) for baseline determinations. In addition, post-dose samples were collected at 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5.5, 5, 6, 8, 10, 12, 14, 16, 18,

24, 36, 48, 72 and 96 hours after dosing. Plasma was extracted and stored frozen pending assay.

Assay Methodology

Free and total ursodiol in plasma were analyzed using a validated method. For the determination of endogenous ursodiol level the firm used "Direct Reading on a Water-Based Standard Curve" technique (Vol. 1.4 page 002121).

Sensitivity: The limit of quantitation (LOQ) was 10 ng/mL for free (unconjugated) ursodiol and 20 ng/mL for total (unconjugated and conjugated) ursodiol.

Linearity: Linear responses were between 20 to 10005 ng/mL for free ursodiol in water. Quality control (QC) samples were prepared with ursodiol-glycine in human plasma at four concentrations (21.2 ng/mL, 62.5 ng/mL, 4042.8 ng/mL and 8043.2 ng/mL, which include the endogenous level of total ursodiol). Endogenous levels in blank plasma for potential use in spiking of QC samples were determined versus a calibration curve in water. The endogenous level was determined to be 42.5 ng/mL. For LLOQ QC samples (21.2 ng/mL) the endogenous level was diluted by factor of 2. All data for ursodiol-glycine or total ursodiol is reported in term of equivalent ursodiol concentrations throughout this study.

Assay specificity: In extracted blank human plasma samples, no significant interference at the retention time of ursodiol-D_4 was observed from endogenous components in any of the 10 blank human plasma screened.

Recovery: The observed recovery of ursodiol-glycine in human plasma was determined

by comparing extracted QC samples at low, medium and high QC concentrations to unextracted calibration standard solutions representing 100% recovery. Mean percent recoveries of ursodiol-glycine in human plasma low, medium and high QC concentrations were 80.6%, 85.2% and 77.4%, respectively.

Precision: Between-batch precision (%CV) results for quality control (QC) samples of ursodiol-glycine in human plasma, prepared at low, medium and high QC concentrations, were 9.7%, 5.8% and 6.8%.

Stability: Freeze/Thaw: Ursodiol-glycine was stable in human plasma unextracted following 5 freeze-thaw cycles.
Long Term Frozen Stability: Ursodiol-glycine was stable in human plasma for 409 days at a nominal temperature of -22°C.

Statistical Methods

Pharmacokinetic parameters for plasma free ursodiol and total ursodiol were calculated for AUC(0-t), AUC(0-24), AUC(0-48), AUC(0-72), AUC(0-96), Cmax and Tmax.
An analysis of variance (ANOVA) was applied to log-transformed and non-transformed bioequivalence parameters to determine any statistically significant ($p<0.05$) differences between the drug formulations. The 90% confidence intervals were calculated for each bioequivalence parameter.

Due to enterohepatic recycling of endogenous ursodiol, no value of Kel, AUCinf or t1/2 could be determined for most subjects as these subjects did not exhibit a terminal log-linear phase in the concentration versus time profile. Therefore, there were insufficient data for comparison of AUCinf in pharmacokinetic and statistical analysis. Consequently, values of kel, AUCinf or t1/2 were not reported.

To correct for the endogenous levels of ursodiol, the post-dose ursodiol concentrations (free and total) were

corrected by subtracting the "average baseline value" from each sampling time point. The "average baseline value" is the calculated mean of the four pre-dose ursodiol (either free or total) concentrations (-24, -17, -10 and 0-hour time points) for each subject across each period. Following the baseline adjustment, all 0-hour (pre-dose) ursodiol concentration (free and total) values were set to zero for "corrected" pharmacokinetic parameters calculation.

Some subjects had baseline plasma free and total ursodiol concentration values that were below the limit of quantitation (BLQ). Because ursodiol is an endogenous bile acid, the BLQ values were set to one-half the lower limit of quantitation (free ursodiol LLOQ = 10 ng/mL; total ursodiol LLOQ = 20 ng/mL) of the assay prior to baseline adjustments.

Due to negative values resulting from the baseline adjustment for some sampling time points in some subjects, the Division of Bioequivalence has determined that only uncorrected ursodiol levels should be considered in bioequivalence studies on ursodiol capsules. It was also determined that it is more appropriate to evaluate total uncorrected rather than free uncorrected ursodiol pharmacokinetic parameters, because of the significant contribution of conjugated ursodiol to total plasma concentrations. The bioequivalence assessment of this study will be based on the current bioequivalence confidence intervals criteria for LnAUC(0-48) and LnCmax. The parameter AUC(0-48) was selected for evaluation because ursodiol plasma concentrations at 72 and 96 hours in many subjects were comparable to pre-dosing concentrations.

IV. In Vivo Results:

Subject #12 was withdrawn from the study by the Medical Advisor after his 24-hour blood draw in period I due to medical events (a para anal abscess not drug related). Subject #19 elected to withdraw from the study after completion of period I due to personal reasons. All adverse events were mild or moderate. No serious adverse events occurred during the study (Vol 1.2, page 000838).

The plasma concentrations and pharmacokinetic parameters for total uncorrected ursodiol are summarized in Table I.

Table I

Mean Total Uncorrected Ursodiol Plasma Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 600 mg Ursodiol (2x300 mg Capsules) Under Fasting Conditions
(N=70)

Time hr	Copley Test Product Lot #380Z03 ng/mL	(CV%)	Novartis Reference Product Lot #166899 ng/mL	(CV%)
0	96.38	(111)	83.91	(108)
0.5	599.98	(97)	500.35	(87)
1	1125.88	(79)	1192.52	(97)
2	1776.45	(62)	1875.99	(59)
2.5	1863.00	(51)	2003.63	(50)
3	1840.55	(45)	2035.14	(40)
3.5	1843.04	(44)	1861.59	(41)
4	1692.94	(44)	1653.93	(43)
4.5	2571.90	(36)	2564.22	(43)
5	2016.21	(56)	1879.29	(51)
5.5	1676.55	(56)	1471.30	(47)
6	1497.00	(49)	1368.39	(39)
8	1002.86	(51)	987.46	(51)
10	1061.00	(45)	1044.25	(54)
12	1040.58	(50)	1076.84	(75)
14	1277.80	(60)	1236.02	(67)
18	873.35	(69)	844.32	(63)
24	504.70	(84)	498.59	(80)
36	709.49	(66)	640.45	(55)
48	300.20	(80)	296.32	(80)
72	262.92	(76)	291.51	(101)
96	224.12	(88)	231.73	(134)

Pharmacokinetic Parameters

	Test	Reference	T/R	90% CI
AUC(0-48) (ng.hr/mL)	40391.8(46)	39120.3(44)	1.03	100.1-107.7%
Cmax (ng/mL)	3158.4(31)	3265.6(37)	0.97	93.0-103.9%
Tmax (hr)	3.6	3.8		

	Mean	SD	Mean	SD	RMSE

LnAUC(0-48)	10.14(0.35)	10.49 (0.43)	0.13
LnCmax	8.01(0.30)	8.03 (0.35)	0.19

1. For Copley's total ursodiol, the mean AUC(0-48) and Cmax values were 3.3%, 3.3% higher and lower, respectively, than those for the reference product values. The 90% confidence intervals are within the acceptable range of 80-125% for log-transformed AUC(0-48) and Cmax.

2. The total ursodiol plasma levels peaked at 4.5 hours for both the test and the reference products following the administration of ursodiol dosing under fasting conditions.

3. Additional analysis of variance was performed by the reviewer, after employing the following model

Y = GRP SEQ SUBJ(SEQ*GRP) PER(GRP) TRT GRP*TRT;

Since the group*treatment effect was not significant, it was dropped from the subsequent ANOVA model used for data analysis.

The following 90% confidence intervals for LnAUC(0-48) and LnCmax were obtained:

Total Ursodiol

LnAUC(0-48)	100.1-107.7%
LnCmax	93.0-103.8%

The 90% confidence intervals for the above pharmacokinetic parameters calculated using the above model remained within the acceptable range of 80-125%.

V. Formulation:

The formulation for Ursodiol 300 mg Capsules is shown in Table II.

VI. In Vitro Dissolution Testing: (USP Method)

Method:	USP 23 apparatus II at 75 rpm
Medium:	1000 mL of phosphate buffer, pH 8.4 with 0.01% sodium lauryl sulfate
Number of Capsules:	12
Test product:	Copley's Ursodiol Capsules 300 mg, lot #380Z03

Reference product: Novartis's Actigall[R] Capsules, 300 mg, lot #166899
Specification: NLT in 30 minutes

Dissolution testing results are shown in Table III.

VII. Comments:

1. The firm's *in vivo* bioequivalence study conducted on its Ursodiol Capsules, 300 mg, under fasting conditions is acceptable. For total uncorrected ursodiol under fasting conditions, the 90% confidence intervals for LnAUC(0-48), and LnCmax are within the acceptable range of 80-125%.
2. The dissolution testing is acceptable.

VIII. Recommendations:

1. The bioequivalence study under fasting conditions conducted by Copley Pharmaceutical, Inc., on its Ursodiol 300 mg Capsule, lot #380Z03, comparing it to Actigall[R] 300 mg Capsule manufactured by Novartis, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Copley's Ursodiol Capsule, 300 mg, is bioequivalent to Novartis's Actigall[R] Capsule, 300 mg.

2. The dissolution testing conducted by Copley Pharmaceutical, Inc., on its Ursodiol 300 mg Capsule, lot #380Z03, is acceptable.

3. The dissolution testing should be conducted in 1000 mL of phosphate buffer, pH 8.4 with 0.01% sodium lauryl sulfate at 37°C using USP 23 apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

> Not less than of the labeled amount of Ursodiol is dissolved in 30 minutes

The firm should be informed of the above recommendations

Moheb H. Makary
Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

BHS 4/12/99
RD INITIALLED BDAVIT
FT INITIALLED BDAVIT Barbara M Davit Date: 4/23/99

Concur: _____ Date: 5/27/99

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Table III. In Vitro Dissolution Testing

Drug (Generic Name): Ursodiol 300 mg Capsules
Dose Strength: 300 mg
ANDA No.: 75-592 Firm: Copley Pharmaceutical, Inc.
Submission Date: February 23, 1999
File Name: 75592SD.299

I. Conditions for Dissolution Testing:

USP 23 Basket: Paddle:X RPM: 75
No. Units Tested: 12
Medium: 1000 mL of phosphate buffer pH 8.4 with 0.01% SLS
Specifications: NLT in 30 minutes
Reference Drug: to Actigall[R] 300 mg Capsule
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 380Z03 Strength(mg) 300			Reference Product Lot # 166899 Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
10	47.6		19.1	54.1		14.6
20	75.2		6.3	74.5		8.3
30	84.2		3.9	82.7		6.3

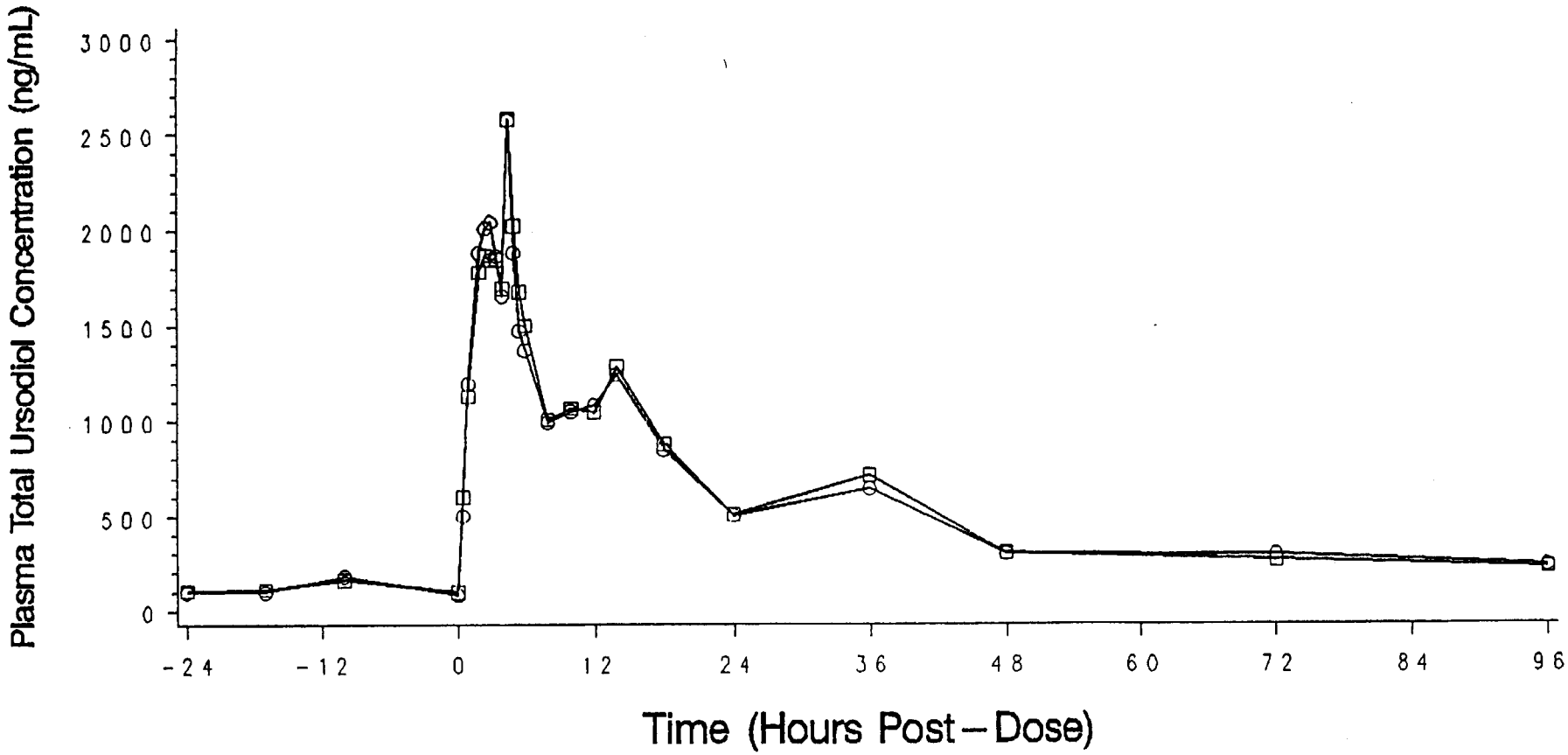
0001007

Figure 6

Project No. 981791

Mean Plasma Total Ursodiol Concentrations (unadjusted)

(Linear Plot)



TOT-RAW (13JAN99)

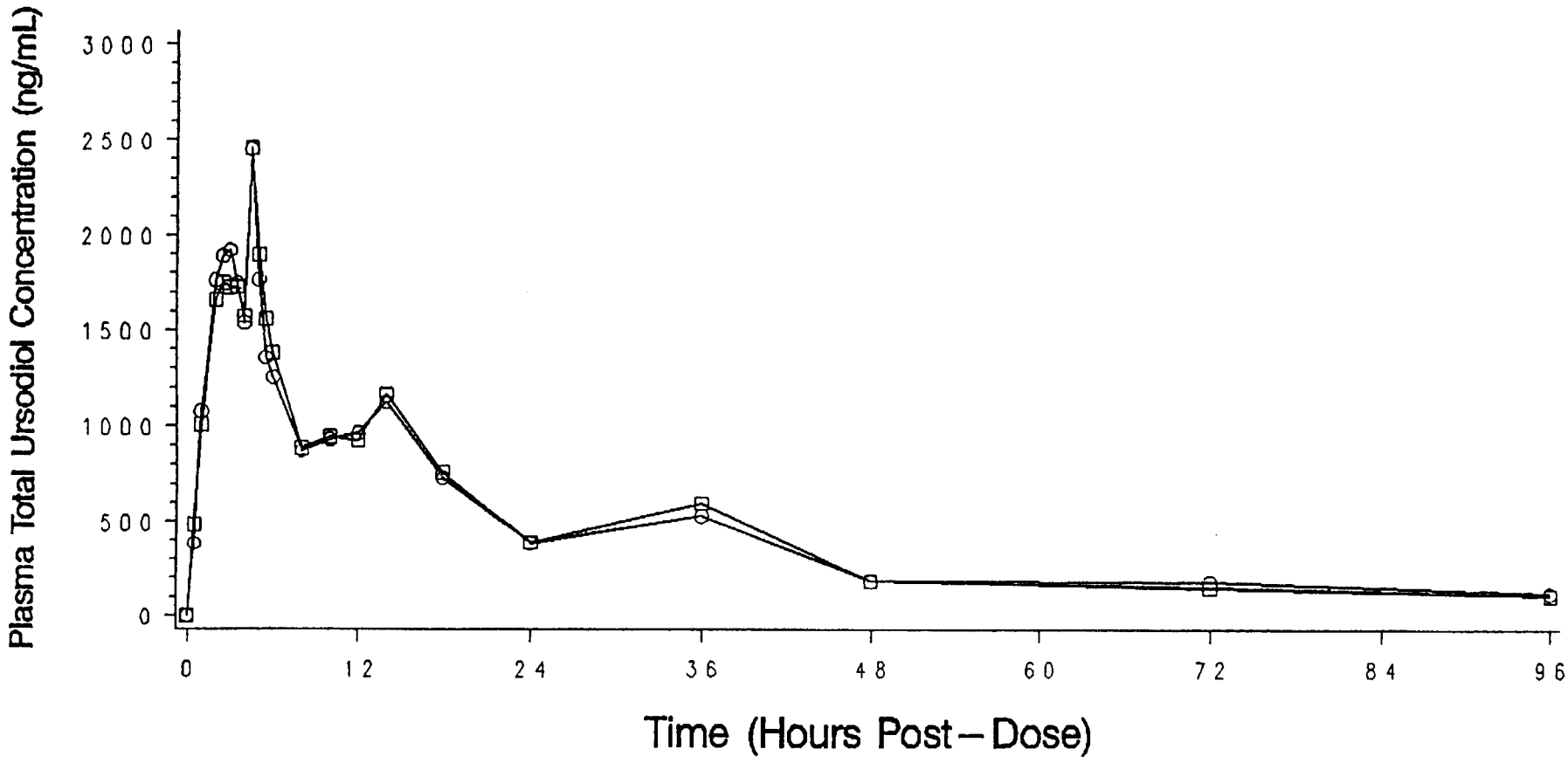
601000

Figure 8

Project No. 981791

Mean Plasma Total Ursodiol Concentrations (adjusted)

(Linear Plot)



TOT-CO2 (13JAN99)

Figure 4

Project No. 981791

Mean Plasma Free Ursodiol Concentrations (adjusted)

(Linear Plot)

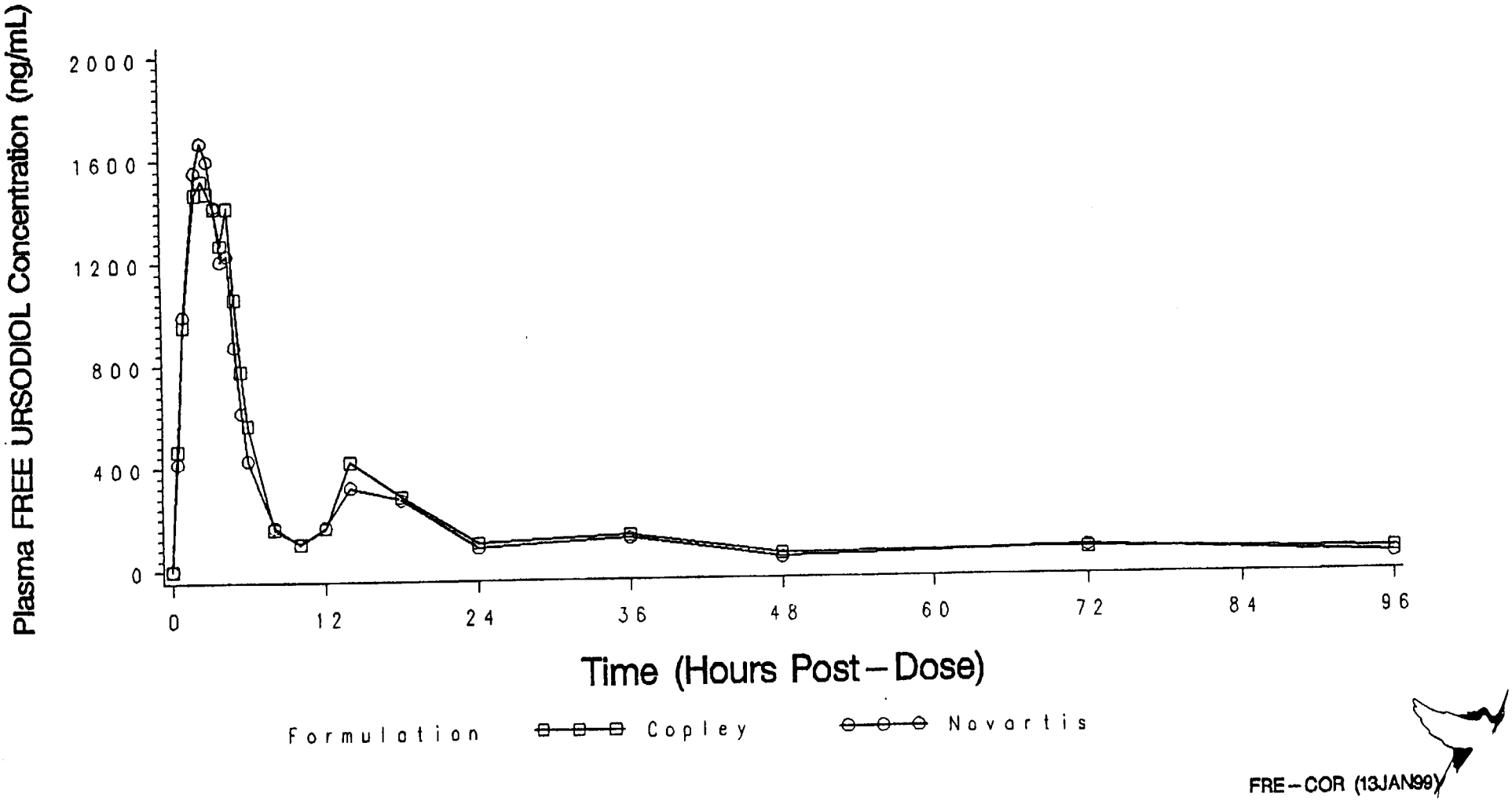
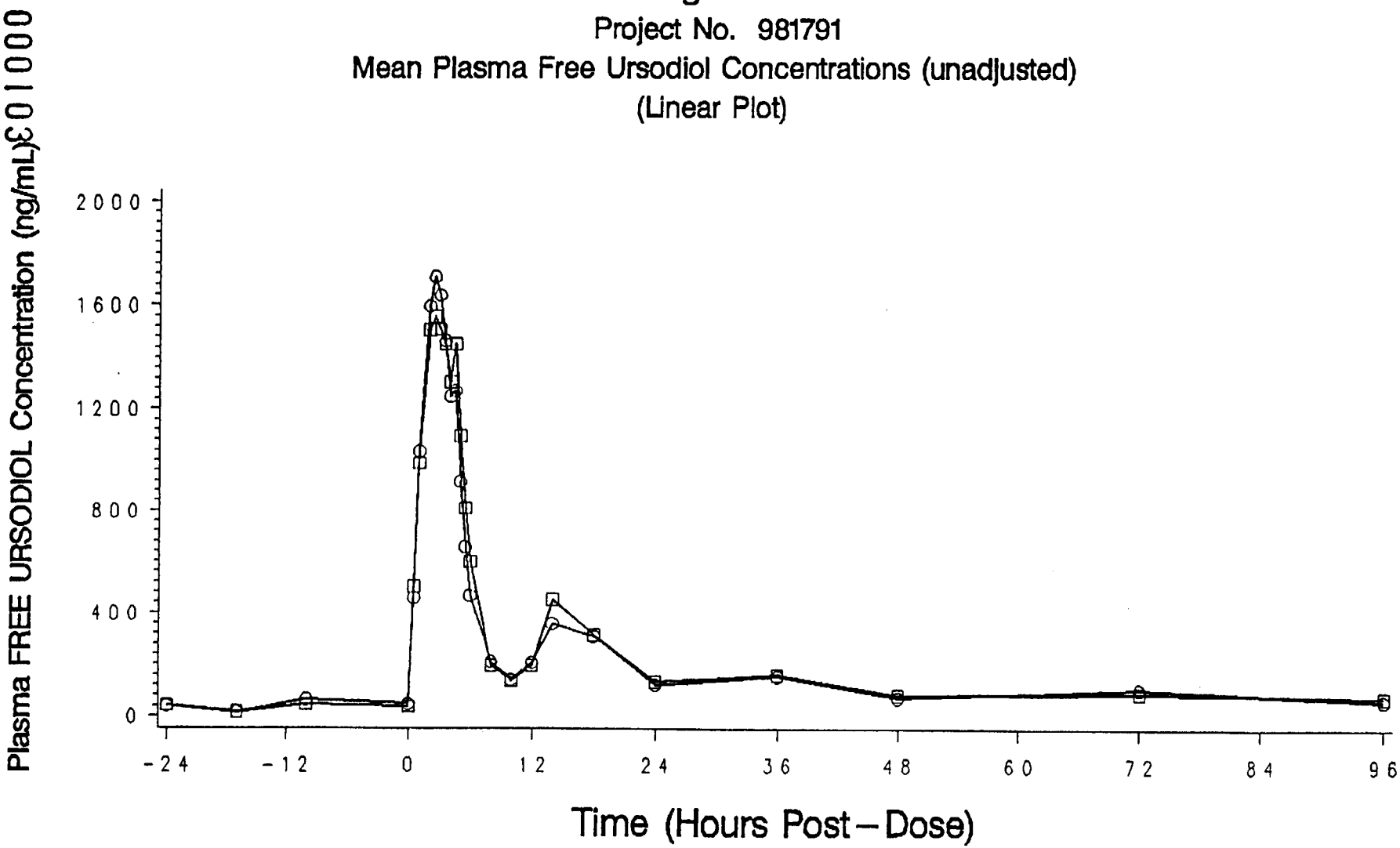


Figure 2

Project No. 981791

Mean Plasma Free Ursodiol Concentrations (unadjusted)

(Linear Plot)



FRE-RAW (13JAN99)

SECTION VII ***Components and Composition Statements***
21 CFR 314.94(a) (9)

2. Composition

A statement of the composition of the drug product

Copley's Ursodiol Capsules, USP 300 mg

COMPONENT	mg/capsule	w/w %	ANDA Demonstration Batch 380Z03 Batch Size: Capsules	Production Scale-Up Batch Batch Size : Capsules
Ursodiol	300.00			
Corn Starch				
il Silicone Dioxide,				
Magnesium Stearate				
Total Theoretical weight				

1.

des.

CENTER FOR DRUG EVALUATION AND RESEARCH

75-592

APPLICATION NUMBER:

ADMINISTRATIVE DOCUMENTS

DIVISION REVIEW SUMMARY

ANDA: 75-592

DRUG PRODUCT: Ursodiol Capsules, USP

FIRM: Copley Pharmaceutical Co.

DOSAGE FORM: Capsules

STRENGTH: 300 mg

CGMP STATEMENT/EIR UPDATE STATUS:
EER Acceptable 6/23/00.

BIO INFORMATION:
The Division of Bioequivalence have found the application to be acceptable on 6/1/99 by M. Makary.

VALIDATION-DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S)
Compendial product. No methods validation needed.

STABILITY-ARE CONTAINERS USED IN THE STUDY IDENTICAL TO THOSE USED IN THE CONTAINER SECTION?

The future stability protocol the firm proposes is as follows:

Test	Limit
Appearance	Red opaque cap printed " _ _ ",, white opaque bottom printed " :" in black ink
Dissolution	NLT of the label amount of Ursodiol is dissolved in 30 minutes
Assay	90.0%-110.0% of label
*Related Substances	NMT NMT ....d NMT NMT NMT

Moisture NMT

*Revised upon request.

The firm included 3 months of accelerated data (40°C/75% RH) for the 100 fill container and 24 months of room temperature data (25 ± 2° C, 60% RH) for lot #380Z03. The testing stations for the room temperature data were abbreviated, (0, 6, 12, 18 and 24 months) and another form containing 0 and 6 months of room temperature data. The firm commits however to test future production batches in accordance with FDA Guidelines. Dissolution appears to be decreasing, in some cases S3 dissolution was used, although specifications were met. The firm states that this is due to the "capsule holder" (it's design and weight). The firm proposes a 24 month expiration dating period. LOQ for the analytical method is NMT = 0.3%.

Also included is a future stability commitment in accordance with FDA Guidelines.

LABELING
The labeling review is satisfactory as of 2/11/00 by A.Vezza.

STERILIZATION VALIDATION
NA

SIZE OF DEMONSTRATION BATCH

A description and flow chart of the manufacturing process is included. The first step of the process involves milling of 2.0 kg of the material through a .. A particle size analysis is performed and the step repeated until the particle size analysis is within established specification. Next the remaining amount of l is passed through the ι. Samples are removed for in-process particle size analysis. The material is collected in double lined drums. If the material does not pass particle size specifications then the material is . The next step involves weighing of , Corn Starch,

and Colloidal Silicon Dioxide . The weighed materials are added

each capsule. Packaging is the final step of the process.

The firm manufactured an exhibit batch (batch #380Z03) of capsules. The Ursodiol USP active was manufacture (batch #8281Z02). The batch was manufactured from 11/5/96 to 12/3/96. The equipment is specified. The firm reports an in-process blend weight yield of (within specification). of the blend was accounted for during encapsulation. The firm manufactured were packaged with 99.9% accountability. The product was packaged into bottles of 100.

Blank batch records are included for future production batches. The intended production size is capsules. The firm includes a summary of equipment and small differences between the exhibit batch and production batch. Essentially the 2 batch records are the same. The firm will begin expiration dating calculation the date of the initial blending of active. A reprocessing statement is also included.

The 9/28/99 amendment included a revised master batch record with minor changes. The main change from the original included addition of a step to combine Corn Starch and Silicon Dioxide together prior to blending with the Ursodiol. This is done to facilitate of the Silicon Dioxide.

PROPOSED PRODUCTION BATCH-MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

See above.

RECOMMENDATION: Approve

SIGNATURE: K Bernard 5/17/00 DATE: 5/3/00
B Hammond 5/22/2000

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 75-592 Date of Submission: February 23, 1999

Applicant's Name: Copley

Established Name: Ursodiol Capsules USP, 300 mg

Labeling Deficiencies:

INSERT

a. GENERAL:

When describing a numerical range, use the word "to" instead of a hyphen.

b. DESCRIPTION

i. Delete "methanol" from the second sentence of the second paragraph.

ii. Revise the second sentence of the second paragraph to read "…acetic acid; slightly soluble in chloroform; sparingly soluble in ether; and practically insoluble…"

iii. The "d" in "3α, 7β-dihydroxy-5β-cholam-24-oic acid." should be capitalized.

iv. The fourth sentence should read as "Ursodiol USP has a molecular weight of 392.58."

v. The fifth sentence of the second paragraph should read as "Its structural formula is…"

c. CLINICAL PHARMACOLOGY

i. Replace "conjugated" with "conjugates" in the seventh sentence of the second paragraph.

ii. The fourth sentence of the third paragraph should read "Man has the capacity…"

iii. Clinical Results (*Gallstone Dissolution*)

The second sentence of the first paragraph should read "…about 30% of unselected patients with…"

d. ALTERNATIVE THERAPIES (Cholecystectomy)

Add "Common duct exploration quadruples the rates in all categories." as the second sentence of the last paragraph.

e. HOW SUPPLIED

Revise to read: "Ursodiol Capsules USP are supplied as…"

Please revise your insert labeling, as instructed above, and submit 4 draft copies of your labels and labeling for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes -

http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

75-592

APPLICATION NUMBER:

CORRESPONDENCE

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068
Direct Tel: (781) 575-7318
Fax: (781) 575-7362

April 27, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP
N / NC hard Copy To Fx

Re: Ursodiol Capsules USP, 300 mg
ANDA 75-592
FAX Amendment to a Pending Application

Dear Mr. Buehler:

Reference is made to Copley's ANDA 75-592 for Ursodiol Capsules USP, 300 mg submitted February 23, 1999, and to your facsimile transmission dated March 28, 2000 (Attachment 1). The Agency's comments have been restated (in bold) and our responses follow.

Chemistry Comments to be Provided to the Applicant

1. **Although, you have revised the limits in your drug substance testing for Related Compounds as requested, we also recommend that you establish a Total impurity limit for Related Compounds, in addition to each of the single Known and Unknown limits in accordance with the drug substance manufacturer's specifications.**

Please refer to Attachment 2 for revised Raw Material Specification for Ursodiol, USP, Document No. , Revision Date 04/12/00, which includes the specifications for Total Impurities (NMT

2. **Regarding your response concerning holding periods, the following comments apply:**

   a.

at

CENTER FOR DRUG ... of ... RECD APR 28 2000 OGD EVALUATION AND RESEARCH

Page(s) 1

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

4/27/00

For stability, the impurity specifications have been changed to NMT for (matching the raw material specification), or individual known impurities, NMT , for individual unknown impurities, and NMT for total impurities (lowered and now matching the raw material specification).

4. **Although you did discontinue the first long term stability study after 6 months in lieu of a second stability study adopting ICH conditions, we are still requesting, due to the dissolution problems encountered, that you submit the 24 month room temperature stability data (ICH conditions) that you have stated are available.**

Please refer to Attachment 7 for an additional copy of Page 005138 of our original ANDA submitted February 23, 1999, which contains the requested 24 month room temperature (ICH conditions) stability data. The batch was tested at stations of 0, 6, 12, 18 and 24 months and passed all tests including dissolution.

We believe that this information satisfactorily addresses all of the deficiencies identified, and request approval of this application.

Please contact Gail Shamsi, RAC, Senior Regulatory Associate at 781-575-7828 or the undersigned at 781-575-7318, should you require any additional information.

Sincerely,

Vincent Andolina

Vincent Andolina, RAC
Sr. Manager, Product Registration

VA: va
Enclosure

h:\ursodiol capsules usp, 300 mg\fax-amendment-20000427.doc

MAR 28

38. Chemistry Comments to be Provided to the Applicant

ANDA: 75-592 APPLICANT: Copley Pharmaceuticals, Inc.

DRUG PRODUCT: Ursodiol Capsules USP, 300 mg

The deficiencies presented below represent FAX deficiencies.

Deficiencies:

1. Although, you have revised the limits in your drug substance testing for Related Compounds as requested, we also recommend that you establish a Total impurity limit for Related Compounds, in addition to each of the single Known and Unknown limits in accordance with the drug substance manufacturer's specifications.

2. Regarding your response concerning holding periods, the following comments apply:

a.

b. Also, since you are proposing a month holding period for the bulk capsules, you should provid months of stability data for the bulk package under controlled room temperature conditions.

3. We also note that you have revised your Impurities specifications for the drug product on release and during stability as requested, however, based on the data provided for exhibit lot #380Z03, we still believe that the levels you are proposing are not supported. Please lower these levels to be more in line with the data or provide further justification for these levels.

4. Although you did discontinue the first long term stability study after 6 months in lieu of a second stability study adopting ICH conditions, we are still requesting, due to the dissolution problems encountered, that you submit the 24 month room temperature stability data (ICH conditions) that you have stated are available.

Sincerely yours,

Vilayat Sayed

for

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

labeling review
drafted 2/10/00
A Vezza

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

September 28, 1999

NDA ORIG AMENDMENT
N/A

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: **Ursodiol Capsules USP, 300 mg**
ANDA # 75-592
Major Amendment to a Pending Application

Dear Mr. Sporn:

Reference is made to Copley's ANDA for Ursodiol Capsules USP, 300 mg submitted February 23, 1999, and to your facsimile transmission dated August 11, 1999 (**Attachment 1**). The Agency's comments have been restated (in bold) and our responses follow.

Chemistry Comments to be Provided to the Applicant

A. **Deficiencies:**

1. **Please be aware that the application ...**

Page(s) 6

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

9/28/99

Labeling Deficiencies

Please refer to **Attachment 12** for final printed container labeling and revised package insert labeling, including a side-by-side comparison of our proposed labeling with our previous submission, with all differences annotated and explained.

B. Revised Master Proposed Record Changes

As indicated in our Response 4, the Master Proposed Record for Ursodiol Granulation for 300 mg Capsules, Weighing and Blending, has been revised. A review of the MPR submitted in the ANDA was conducted and a few minor changes were determined to be necessary. The primary change involves the addition of a step to

A chart outlining the minor changes to the MPR and the justification for the changes is provided in **Attachment 13**. The revised Master Proposed Record for Ursodiol Granulation for 300 mg Capsules, Weighing and Blending is provided in **Attachment 5**.

We believe that this information should satisfactorily address all of the deficiencies identified.

Please contact Gail Shamsi, Senior Regulatory Associate at 781-575-7828 or the undersigned at 781-575-7695, should you require any additional information.

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs

Enclosure

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-592 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Ursodiol Capsules, 300 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

AUG 11 1999

Chemistry Comments to be Provided to the Applicant

ANDA: 75-592 APPLICANT: Copley Pharmaceuticals, Inc.

DRUG PRODUCT: Ursodiol Capsules USP,300 mg

The deficiencies presented below represent MAJOR deficiencies.

A. Deficiencies:

1. Please be aware that the application cannot be approved until deficiencies regarding DMF have been addressed satisfactorily by the holder.

2. It is recommended that you establish a Single Identified and Unidentified Impurity limit in your drug substance testing for Urosodiol.

3. Your testing for does not appear to be in full accordance with current compendia. See USP 23. Supp. 10.

4. The batch records include an instruction that states if

5. It is noted that batch #380Z03 was manufactured over the course of several weeks. In accordance with 21 CFR, please clarify if you have established reasonable time limits on production, specifically with regard to holding periods during each of the major steps of the manufacturing process, including the

6. We also recommend that you establish a reasonable specification limit for Single Known Impurities as well as Unknown Impurities in your release and stability testing for Related Substances for the drug product.

7. Regarding the related substances method we have the following comments:

   a. Page 005090 includes two USP 23 methods where one is shown to elute at an RT

of approximately 8-9. The two sample _ included utilizing your method do not include a peak for Epiandrosterone. You should re-run the _ with a spiked sample of

b. It is unclear why you do not include _ in your list of impurities for Urosodiol on page 005086.

c. Please clarify why you adjust the attenuator from 64 for assay to 8 for related substances.

d. Page 005088 illustrates 2 impurities eluting at less than 4.0 minutes, however page 005036 indicates that you inhibit the _ at 4.0 minutes. Please clarify.

e. It is recommended that the sensitivity related compounds methods be improved.

8. We acknowledge that you intend to utilize your own analytical methods for the drug product. Please be aware however, that if a dispute should occur in the future, we consider the USP method to be the preferred regulatory method.

9. Regarding the sharp decrease in dissolution seen during stability for this product, you have stated that this seems to be due to the capsule holder used. You are requested to expand on this and provide data to justify your argument if possible. We would also like you to provide assurance that this will not be a concern with this product in the future.

10. Also, since the capsules do appear to display a decrease in dissolution on stability, you are requested to provide the remaining room temperature data that is available corresponding to the report format submitted on page 005139.

11. We also note that the analytical method for Related Substances used during stability has an LOQ = 0.3%, however the data show single impurities measurements of 0.2%, less than and about 0.2%. Since the LOQ is 0.3%, impurities detected at less than the LOQ, should be reported as less than LOQ. We believe that the stability data measurements you included are not considered accurate if the LOQ for the method is 0.3% and should be revised.

12. You should also lower your proposed Impurities specifications on release and during stability for the drug product. The stability data submitted for lot #380Z03 do not support the levels you have proposed.

Sincerely yours,

Florence S. Fang
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-592 APPLICANT: Copley Pharmaceutical, Inc.

DRUG PRODUCT: Ursodiol Capsules, 300 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-592

Copley Pharmaceutical, Inc.
Attention: I. Nudelman
25 John Road
Canton, MA 02021

MAR 16 1999

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to our telephone conversation dated March 5, 1999 and your correspondence dated March 9, 1999.

NAME OF DRUG: Ursodiol Capsules USP, 300 mg

DATE OF APPLICATION: February 23, 1999

DATE (RECEIVED) ACCEPTABLE FOR FILING: February 25, 1999

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,
Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

March 9, 1999

505(b)(2)(A) OK
3/15/99
NEW CORRESP
NC

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MG 20855-2773

Controlled Correspondence
Ursodiol Capsules, USP 300 mg
ANDA # 75-592

Dear Mr. Sporn:

Reference is made to the above Abbreviated New Drug Application for Ursodiol Capsules, USP 300 mg submitted to the Agency on February 24, 1999 and to the telephone conversation with Mr. Gregory Davis, Project Manager, Regulatory Support Branch, O.D.G., and I. Nudelman, Director Regulatory Affairs with Copley Pharmaceutical, Inc., on March 5, 1999.

Mr. Davis indicated that upon review of the above referenced ANDA, O.D.G. requires the "Certification of Financial Interests and Arrangements of Clinical Investigators" Form completed and signed.

Accordingly please find enclosed the requested Form FDA 3454, listing the clinical investigators who participated in the clinical study entitled: "Comparative, Randomized, 2-Way Crossover Bioavailability Study of Copley and Novartis (Actigall®) 300 mg Ursodiol Capsules, Following Administration of a 600 mg Dose, Under Fasting Conditions" conducted by :
and included in ANDA # 75-592.

Should you have any questions or concerns please fell free to contact me at the numbers given below.

Sincerely,

I Nudelman, RAC
Director, Regulatory Affairs
Direct dial:1-781-575-7695, Fax:1-781-575-7362

attachments

RECEIVED
MAR 10 1999
GENERIC DRUGS

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

March 5, 1999

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER (HFD600)
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MG 20855-2773

NEW CORRESP
NC

Controlled Correspondence
Ursodiol Capsules, USP 300 mg
ANDA # 75-592

Dear Mr. Sporn:

Reference is made to the above Abbreviated New Drug Application for Ursodiol Capsules, USP 300 mg submitted to the Agency on February 24, 1999 and to the telephone conversation with Mr. Gregory Davis, Project Manager, Regulatory Support Branch, O.D.G., and I. Nudelman, Director Regulatory Affairs with Copley Pharmaceutical, Inc., on March 5, 1999.

Mr. Davis indicated that upon review of the above referenced ANDA O.D.G. requires additional copies of the Copley's Ursodiol Capsules, USP 300 mg draft labeling.

Accordingly please find enclosed three additional copies of our package insert labeling (pages 41-A to 49-C) and container labeling (pages 51-A to 51-C).

In addition under separate cover we will provide Certification for Financial Interests and Arrangements of Clinical Investigators.

Should you have any questions or concerns please fell free to contact me at the numbers given below.

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs
Direct dial:1-781-575-7695, Fax:1-781-575-7362

attachments

RECEIVED
MAR 0 8 1999
GENERIC DRUGS

Copley Pharmaceutical Inc.

25 John Road
Canton, Massachusetts 02021
(781) 821-6111
Mailroom Fax: (781) 821-4068

February 23, 1999

Mr. Douglas Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA Submission
Ursodiol Capsules, USP 300 mg

Dear Mr. Sporn

Copley Pharmaceutical, Inc. (Copley) submits an original Abbreviated New Drug Application (ANDA) seeking approval to market Ursodiol Capsules, USP 300 mg. The listed drug, Actigall® (Ursodiol) Capsules, USP 300 mg is manufactured by , and distributed by Novartis Pharmaceuticals Corporation, East Hanover, NJ, under its approved New Drug Application No. 19-594.

Copley completed the bioequivalence study on the Ursodiol Capsules, USP 300 mg entitled: "Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of Copley and Novartis (Actigall®) 300 mg Ursodiol Capsules, Following Administration of a 600 mg dose, Under Fasting Conditions". The bioequivalence study report was designed and conducted with consideration to applicable Agency guidelines and expectations. The data demonstrate our product to be equivalent to the branded product and therefore we request an AB rating in FDA's listing of Approved Drug Products with Therapeutic Equivalence Evaluations. The bioequivalence trial was conducted by

This application is submitted in accordance with the guidelines set forth in Section 505(j) of the Federal Food, Drug, and Cosmetic Act. The application consists of nine (9) volumes which are numbered sequentially: Volume 1 contains Section I-XXI and Volumes 2 to 9 contain the bioequivalence study.

According to 21 CFR § 314.94 (a) (13) and to the Agency's letter of January 20, 1999, the new "Financial Statement" prepared by :., is included in Section III.

RECEIVED
FEB 25 1999
GENERIC DRUGS

Copley is submitting a complete archival copy (in "blue jackets") of the ANDA which contains all required information in such an application. In addition, we are submitting the following segments: a technical review copy (in "red jackets") containing all sections with the exception of Section VI; a technical review copy, Bioequivalence (in "orange jackets") containing Sections I-VII, including Section VI containing the in vivo bioequivalence study report and a diskette containing the "Total Ursodiol, Uncorrected Baseline and Corrected Baseline, Free Ursodiol, Uncorrected Baseline and Corrected Baselines" spreadsheets which are located in Volume 2.

Two (2) additional, separately bound copies of the analytical methods and validation package containing Sections XVI-XXI, to support FDA's analytical testing of the drug product, are provided in two "black jackets."

Copley certifies that, concurrently with the submission of this ANDA, a true copy of the technical sections of the ANDA will be forwarded to the Food and Drug Administration, New England District Office. The "field copy" is contained in nine "burgundy jackets."

Should you have any questions regarding this application, please contact the undersigned at 1-781-575-7695.

Thank you for your prompt handling of this submission.

Sincerely,

I. Nudelman, RAC
Director, Regulatory Affairs

Enclosures:

Archival Copy (nine "blue jackets")
Review Copies (one "red" and eight "orange jackets")
Analytical Methods and Validation Package (two "black jackets")