CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-517

Approval Letter

ANDA 75-517

MAR 14 2000

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

Dear Sir:

This is in reference to your abbreviated new drug application dated December 7, 1998, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Ursodiol Capsules USP, 300 mg.

Reference is also made to your amendments dated January 19, April 19, August 4, September 30, and November 30, 1999, and March 7, 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 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 which 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,

/S/ J. Woodcock, M.D.
3/14/00
Refer to administrative sign-off sheet

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-517

FINAL PRINTED LABELING

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 stone > 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 in 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.

Stones 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, or 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***

	Age (Yrs)	Cholecystectomy	Cholecystectomy + Common Duct Exploration
Low Risk Patients*			
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 rate in all categories. The rate 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 stone < 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

Liver Tests

Ursodiol therapy has not been associated with liver damage. Lithocholic acid, a naturally occurring bile acid, is known to be a liver-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 sulfator, 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 taurodeoxycholic 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 coadministered 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:

GALLSTONE DISSOLUTION

	Ursodiol 8 to 10 mg/kg/day (N=155)		Placebo (N=150)	
	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)

MAY 14

Amide
PHARMACEUTICAL, INC.

NDC 52152-060-05

URSODIOL CAPSULES, USP 300 mg

Rx only

1000 CAPSULES

Each Capsule Contains:
Ursodiol ..... 300 mg

Usual Dosage: See Accompanying Literature.

This is a bulk container. Not intended for household use.

Dispense in a tight, light-resistant container as defined in the USP.

Store at controlled room temperature 15° to 30°C (59° to 86°F) (see USP).

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

N 3 52152-060-05 1

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.:
Exp. Date:
8005-01

Amide
PHARMACEUTICAL, INC.

NDC 52152-060-02

URSODIOL CAPSULES, USP 300 mg

Rx only

100 CAPSULES

Each Capsule Contains:
Ursodiol ..... 300 mg

Usual Dosage: See Accompanying Literature

Dispense in a tight, light-resistant container as defined in the USP

Store at controlled room temperature 15° to 30°C (59° to 86°F) (see USP)

KEEP THIS AND ALL MEDICATION OUT OF THE REACH OF CHILDREN.

AMIDE PHARMACEUTICAL, INC.
101 East Main Street
Little Falls, NJ 07424 USA

Control No.
Exp. Date
8004-01

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/kg given 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/ Pink Opaque, filled gelatin capsules, with imprint "A-060" on cap and body and are available in bottles of 100's and 1000's.

Store at controlled room temperature 15° to 30°C (59° to 86°F) (see USP).

Dispense in a tight, light-resistant container as defined in the USP.

7/99

MANUFACTURED BY
AMIDE PHARMACEUTICAL, INC.
101 East Main Street Little Falls, NJ 07424 USA

Rx Only

Prescribing Information

7952-01

URSODIOL CAPSULES, USP

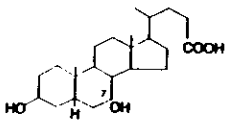
SPECIAL NOTE

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 USP (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 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. Its molecular formula is ($C_{24}H_{40}O_4$) and molecular weight is 392.58. Its structural formula is as follows:



Inactive ingredients. Corn starch, magnesium stearate, silicon dioxide and the capsule shell contains the following ingredients, D&C Red #28, D&C Yellow #10 Aluminum lake, FD&C Blue #1 Aluminum lake, FD&C Blue #2 Aluminum lake, FD&C Red #40 Aluminum lake, Gelatin NF, Pharmaceutical glaze (modified) in SD-45, Synthetic Black Iron Oxide, 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 gall bladder 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 acid (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 does (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.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-517

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. **2**

2. ANDA # **75-517**

3. NAME AND ADDRESS OF APPLICANT
Amide Pharmaceutical, Inc.
101 East Main Street
Little Falls, NJ 7424

4.

Generic version of Giuliani S.p.A., ACTIGALL® (NDA 19-594). Patent certification and exclusivity statement are provided (pp. 012-015)

Innovator Company: Giuliani for Novartis
Patent Expiration Date: March 29, 1999

5. SUPPLEMENT(s) **N/A**

6. PROPRIETARY NAME
Ursodiol

7. NONPROPRIETARY NAME
URSODIOL CAPSULES

8. SUPPLEMENT(s) PROVIDE(s) FOR: **Original ANDA**

9. AMENDMENTS AND OTHER DATES:

Firm			**FDA**	
Orig. submission		9/18/98 8		
New correspondence		12/17/98	Acknowledgment letter	12/29/98
Amendment		1/19/99	Bio review	3/9/99
			Bio deficiency letter	3/24/99
Amendment	(Bio)	4/19/99	Bio review acceptable	6/8/99
			Deficiency letter (minor)	6/30/99
Amendment	(minor)	9/30/99		
Amendment	(phone)	11/30/99		

This review covers submissions dated 9/30 and 11/30/99

10. PROPOSED INDICATION(S) FOR USE
Management and prevention of Gall Stones

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

DMF number	DMF type	LOA(s)

13. DOSAGE FORM
Capsule

14. STRENGTH(S)
300 mg

15. CHEMICAL NAME AND STRUCTURE
Cholan-24-oic Acid, 3-7-dihydroxy-3d, 7B-Dihydroxy-5B-cholan-24-oic acid.

16. RECORDS AND REPORTS N/A
The drug substance and drug product are monographed in USP 23, Supplement #2.

17. COMMENTS
a. Application is satisfactory for approval
b. Labeling review is satisfactory, dated 10/13/99
c. Bio review found adequate, dated 6/14/99
d. found adequate, dated 10/27/99
e. Methods validation is not required, both drug substance and drug product are compendial.
f. Establishment Evaluation Request found acceptable, dated 6/2/99.

18. CONCLUSIONS AND RECOMMENDATIONS
APPROVE

19. REVIEWER:
Raymond Brown

DATE COMPLETED:
January 12, 2000

Page(s) 11

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Chemistry Review #2

1/12/00

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

6/30/99

Chemistry Comments

#38.

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-517

BIOEQUIVALENCE REVIEW(S)

DIVISION REVIEW SUMMARY

ANDA 75-517 **DRUG PRODUCT:** Ursodiol

FIRM: Amide Pharmaceuticals, Inc. **DOSAGE FORM:** Capsules

STRENGTH: 300 mg

CGMP STATEMENT/EIR UPDATE STATUS: Acceptable -
Dated June 2, 1999.

BIO INFORMATION: Adequate -
See bio review, dated 6/14/99.

VALIDATION-(DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): N/A -

STABILITY: Satisfactory -
Accelerated (40°C/75 RH) stability data are provided for batch no. 6123A, tested initially, 4, 8 and 12 week intervals in the upright position. Controlled room temperature (25-30°C/Ambient Humidity) stability data are also provided, tested 3, 6, 9, 12, 18 and 24 month intervals.

LABELING: Acceptable -
See Review of professional labeling, dated 10/13/99.

STERILIZATION VALIDATION: N/A -

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?) Satisfactory -
Bio batch no. 6123A, actual yielded capsules. Bulk substance manufacturer , batch no. C065N097 used. found ADEQUATE 10/27/99.

SIZE OF STABILITY BATCHES - Satisfactory -
Executed Batch Manufacturing Documents are provided for batch no. 6123A, which consist or capsules. The batch was manufactured using production equipment under production conditions.

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

The proposed master production batch sizes are apsules, capsules and capsules.

RECOMMENDATION:
APPROVE

/S/
Raymond Brown

1/18/00
Date

cc:

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-517 APPLICANT: Amide Pharmaceutical, Inc.

DRUG PRODUCT: Ursodiol 300 mg capsule

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, 2nd suppl.

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,

/S/

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

Ursodiol
300 mg capsule
ANDA #75-517
Reviewer: J. Lee
75517STA.499

Amide Pharmaceutical, Inc.
Little Falls, New Jersey
Submission date:
April 19, 1999

Review of a Study Amendment

This submission contains the responses to the deficiencies issued to the sponsor in the review of the original bio-study (rev. 9 March 99).

1. The sponsor did not submit the complete analytical method for unconjugated and total ursodiol and was requested to do so.

2. In the analysis of **total ursodiol**, the sponsor was asked to explain why two sets of QC samples were prepared and run when it was noted that there was only one set of corresponding calibration curve standards.

☞ The sponsor explained that an additional QC sample (unconjugated ursodiol) was added to one of the QC sets to demonstrate completion of hydrolysis.

3. The sponsor was requested to explain why ursodiol-glycine was used in the spiking of QC samples in the analysis of total ursodiol.

☞ The sponsor explained that during R & D, it was demonstrated that the hydrolysis of ursodiol glycine and/or taurine was complete and equivalent; ursodiol glycine was chosen as it was readily available and a COA could be provided.

4. Long term stability data to cover the length of the entire study was requested for **unconjugated ursodiol**.

☞ Acceptable long term stability data that covered 375 days @ -22°C was provided.

5. Long term stability data was also requested for **total ursodiol**.

☞ Acceptable long term stability data for ursodiol-glycine that covered 409 days @ -22°C was provided.

6. The sponsor was requested to document lack of interference at the rentention time of the internal standard for both unconjugated and total ursodiol analyses.

☛ Documentation of potential interference from endogenous compounds or possible degradation products at the retention time of the IS for total ursodiol was evaluated as part of another previous project. Because no interferences were observed in that project, further investigation was not conducted for the IS for unconjugated ursodiol, since both assays employed the same internal standard.

7. Potency/content uniformity data was not provided for the reference product used in this study. The sponsor was requested to submit such data.

☛ The comparative data is as follows:

	Potency	C.U.
Amide		
Actigall		

8. The sponsor was requested to submit on diskette all baseline uncorrected subject data for both unconjugated & total ursodiol.

☛ The sponsor has complied with the request. Additional analyses and confirmatory analyses were performed on all datasets.

Comment:

1. The sponsor has satisfactorily addressed all deficiencies.

Recommendation:

1. The bioequivalence study conducted by for Amide Pharmaceutical, Inc. on its ursodiol 300 mg capsule, batch #6123A, comparing it to Actigall® 300 mg capsule has been found acceptable by the Division of Bioequivalence.

2. The in-vitro dissolution testing data (USP) is also acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 ml of phosphate buffer pH 8.4 at 37°C using USP XXIII apparatus II (paddle) at 75 rpm. The test product should meet the following specification:

3. All bioequivalence criteria have been met.

R. Lee 6/8/99

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR 6/8/1999

Concur: /S/ Date: 6/14/99

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

JLee/jl/06-08-99

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-517 APPLICANT: Amide Pharmaceutical, Inc.

DRUG PRODUCT: Ursodiol 300 mg capsule

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, 2nd suppl.

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,

/S/

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

Amide PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

April 19, 1999

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

Orig.

AB

Bioequivalency Amendment

RE: ANDA - 75-513
Ursodiol Capsules USP

Dear Mr. Sporn:

In response to the Bioequivalency deficiency letter dated March 24, 1999, enclosed find our response as follows:

For Items 1 to 6, find response in Attachment I.

For Item 7.:
Potency/Content Uniformity data was not provided for the reference product used in this study . Please submit data.

Response: Enclosed find the requested data in Attachment II, [Comparative product profile for Ursodiol Capsules for Amide's and Novartis (Actigal)].

Item 8.:
Please submit on diskette all baseline uncorrected subject data for unconjugated and total ursodiol [including period, sequence, treatment for the PK parameters and the individual sample concentration values for each subject arranged sequentially in a flat ASCII text format]; baseline values as well as the zero hour value (before baseline corection) for each subject should also be included in the dataset.

Response: Attached is a diskette including the data requested.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

Enc.

RECEIVED
APR 20 1999
GENERIC DRUGS

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:75-517 APPLICANT: Amide Pharmaceuticals MAR 24 99

DRUG PRODUCT: Ursodiol 300 mg capsule

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. The complete analytical method was not submitted. Please submit the standard and QC sample preparation procedure as well as sample, standard, and QC processing procedures for both unconjugated ursodiol [SOP No. GC-M-5841-00] and total ursodiol [SOP No. GC-M-5862-01].

2. In the analysis of **total ursodiol**, explain why two sets of QC samples were prepared and run as noted on page 1435 of vol. 1.4 (covering curve code HUD 13-53) and on page 1437 of vol. 1.4 (covering curve code HUD 56-74). It was noted that there was only one set of corresponding calibration curve standards (pp 1438-40, vol. 1.4).

3. Please explain why ursodiol-glycine was used in the spiking of QC samples in the analysis of total ursodiol.

4. Samples were analyzed for **unconjugated ursodiol** between Jan 5, 1998 and Oct 26, 1998; yet long term stability data was provided for a period of only 21 days. You need to provide long term stability data to cover the length of the entire study.

5. Long term stability data was not submitted for **total ursodiol**. Please submit such data that covers the duration of the study.

6. You did not provide the raw data for 'C_{max}' samples to document lack of interference at the retention time of the internal standard. Please provide such documentation for both the unconjugated and total ursodiol analyses.

7. Potency/content uniformity data was not provided for the reference product used in this study. Please submit such data.

8. Please submit on diskette all baseline uncorrected subject data for unconjugated and total ursodiol [including period, sequence, treatment for the PK parameters and the individual sample concentration values for each subject arranged sequentially in a flat ascii text format]; **baseline values** as well as the zero hour value (before baseline correction) for each subject should also be included in the dataset.

Sincerely yours,

/S/

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

Ursodiol
300 mg capsule
ANDA #75-517
Reviewer: J. Lee
75517SD.199

Amide Pharmaceutical, Inc.
Little Falls, New Jersey
Submission date:
December 7, 1998
January 19, 1999

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

Background:

Ursodiol (ursodeoxycholic acid) is a naturally occurring bile acid normally found in small quantities in human bile. Ursodiol suppresses the synthesis and secretion of cholesterol by the liver, inhibits intestinal absorption of cholesterol, and can dissolve cholesterol-rich gallstones in some patients. It is indicated as an alternative to surgery for the treatment of radiolucent, noncalcified gallbladder stones less than 20 mm in diameter. The recommended dose is 8 - 10 mg/kg/day, given in 2 or 3 divided doses.

Approximately 90% of a dose of ursodiol is absorbed after oral administration. About half of the absorbed drug is immediately removed from the blood by first-pass hepatic extraction and conjugation and is excreted into the bile.

There is little information in the literature about the pharmacokinetics of unconjugated ursodiol in plasma after a single oral dose. The major route of excretion for ursodiol and its metabolites is the feces.

Study Design:

The clinical study (#971230) was conducted at in
under the supervision of Principal Investigator.

Twenty-four healthy adult male volunteers (plus 2 alternates) between the ages of 18-45 years and within 15% of ideal body weight for his height and frame were selected for the study.

All selected volunteers were in good health as determined by a medical history, physical examination and clinical laboratory tests and an HIV test. All were judged acceptable according to protocol.

The study was designed as a randomized, open-label two-way crossover study with a 4 week washout period between dosings. Treatments consisted of a single 600 mg dose of the following:

A. Ursodiol
300 mg capsule, batch #6123A2 (2 x 300 mg)
Amide Pharmaceutical, Inc.

expiry date: not given

B. Actigall*
300 mg capsule, batch #1432 (2 x 300 mg)
Novartis
expiry date: June, 1998

Twenty-six subjects were dosed according to the following regimen:

	Period I 11/21/97	Period II 12/19/97
sequence I	A	B
sequence II	B	A

sequence I - subj. # 1, 2, 3, 6, 8, 10, 11, 12, 14, 16, 19, 21, 25
sequence II - subj. #4, 5, 7, 9, 13, 15, 17, 18, 20, 22, 23, 24*, 26

*Subj. #24 withdrew from the study following per I for personal reasons.

After an overnight fast, subjects were given a 600 mg dose of ursodiol with 240 ml of water. Fasting continued for 4 hours post-dose. Blood samples (5 ml) were drawn in Vacutainers containing EDTA at –24, -12, 0 (pre-dose), 0.5, 1, 1.5, 2. 2.5. 3, 3.5, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48 and 72 hours. All blood draws were taken within 2 minutes of scheduled sampling time, except for those listed in table C2 of the Clinical Report. Those deviations, however, were insignificant.

There were a total of 22 medical events reported of which 10 (5 test/5 ref) were possibly/probably related to the study drug [headache, nausea, stomachache, etc.]. Several volunteers were given Tylenol. All events were non-serious.

There were a few deviations from protocol reported in this study, centering mainly around diet-related infractions. All deviations were judged unlikely to affect the bioavailability comparison.

Analytical: [Not for release under FOI]

The plasma samples were assayed for unconjugated and total ursodiol by high resolution GC/MS methods developed by Details of the sample preparation processes were not included in the analytical validation reports [SOP No. GC-M-5841-00, (unconjugated ursodiol) and No. GC-M-5862-01 (total ursodiol)]

Quantitation of drug levels was based on peak area ratios of ursodiol (unconjugated and total) to internal standard vs nominal standard concentration, using a linear regression weighted by 1/conc.

Unconjugated Ursodiol

Standards were prepared in water in the concentration range of 10.0 – 2500 ng/ml (8 points) for the calibration curve. The sensitivity of the assay (LOQ) was chosen at 10.0 ng/ml, the concentration of the lowest non-zero standard. Sample concentrations with no significant peak at the retention time of ursodiol or with peak area ratios below that of the LOQ were reported as BLQ (below the limit of quantitation).

The coefficient of correlation (r) was ≥0.9939 for the standard curves. The coefficient of variation for the standards ranged from 3.3% (at 2250 ng/ml; n=31) to 7.3% (at 10.1 ng/ml; n=27).

The precision of the assay was monitored by the quality control samples that were run in duplicate with each group of samples. This data showed:

QC Value	Mean	%CV
41.50 ng/ml (n=57)	45.81	11.1
1011 ng/ml (n=60)	1001	6.1
2010 ng/ml (n=60)	1974	6.9

Stability data submitted in the analytical validation package showed no decline in ursodiol plasma concentrations [at 33.56 and 2004 ng/ml; n=10] after a 21 day period under frozen conditions (-22°C). In a separate studies, stability samples showed no decline in ursodiol for benchtop stability (16.5 hrs @ RT) nor freeze-thaw stability (4 cycles) at the same two concentrations mentioned above.

Recovery data for ursodiol showed the following:

45.3% at 33.56 ng/ml (CV=3.6%; n=10)
48.2% at 1004 ng/ml (CV=1.9%; n=10)
48.9% at 2004 ng/ml (CV=1.9%; n=10)

Recovery data for the internal standard:

48.8% at 1.26 mcg/ml (CV=3.9%; n=10)

Total Ursodiol

Standards were prepared in water in the concentration range of , ng/ml (9 points) for the calibration curve. The sensitivity of the assay (LOQ) was chosen at 17.1 ng/ml, the concentration of the lowest non-zero standard. Sample concentrations with no significant peak at

the retention time of ursodiol or with peak area ratios below that of the LOQ were reported as BLQ (below the limit of quantitation).

The coefficient of correlation (r) was ≥0.9960 for the standard curves. The coefficient of variation for the standards ranged from 2.9% (at 7703 ng/ml; n=30) to 11.0% (at 17.1 ng/ml; n=31).

The precision of the assay was monitored by the quality control samples that were run in duplicate with each group of samples. QC samples were spiked with ursodiol-glycine. Final concentrations were reported as ursodiol concentration. This data showed:

QC Set 1 [covering standard curves HUD 13-53]

QC Value	Mean	%CV
81.01 ng/ml (n=38)	79.59	10.1
3451 ng/ml (n=42)	3254	6.7
6872 ng/ml (n=42)	6460	5.7

QC Set 2 [covering standard curves HUD 56-74]

QC Value	Mean	%CV
77.04 ng/ml (n=19)	74.92	7.3
3451 ng/ml (n=19)	3256	5.6
6872 ng/ml (n=19)	6670	4.5

Stability data submitted in the analytical validation package showed no decline in ursodiol plasma concentrations for benchtop stability (20.5 hrs @ RT) and freeze-thaw stability (3 cycles) at 75.97 and 6860 ng/ml. Long term stability was reported to be 'in progress'.

Recovery data for ursodiol-glycine showed the following: [reported as ursodiol]

67.6% at 75.97 ng/ml (CV=4.8%; n=10)
61.05% at 3442 ng/ml (CV=2.2%; n=10)
58.14% at 6860 ng/ml (CV=1.9%; n=10)

Recovery data for the internal standard (ursodiol D_4):

72.0% at 2.14 mcg/ml (CV=12.1%; n=10)

Since ursodiol is an endogenous substance, blood levels of ursodiol were baseline corrected and zero hour samples were set to zero.

Data Analysis:

Plasma data was analyzed by an analysis of variance procedure (SAS, ver 6.04) to determine statistically significant ($p<0.05$) differences between treatments, sequence of dosing, subjects within sequence and periods for the pharmacokinetic parameters. Twenty-five of the twenty-six enrolled subjects completed the crossover; twenty-four datasets were analyzed, per protocol. [Samples from subj #25 were not analyzed]. Due to enterohepatic recycling, a reasonable AUC_{inf} could not be obtained for most of the subjects. AUC_{0-24}, AUC_{0-48} and AUC_{0-72} were used instead.

Results:

No statistically significant differences were found in any of the major pharmacokinetic indices, on the ln-transformed scale for both unconjugated and total ursodiol. **Sequence effects**, however, were observed for unconjugated ursodiol in AUC_{0-24} and in C_{max} parameters. For unconjugated ursodiol there was a 2.6% difference between the test and reference formulations for plasma levels of ursodiol in AUC_{0-24}, AUC_{0-48} and AUC_{0-72} and a 6.7% difference in C_{max}. For total ursodiol there was a 7.4% difference between the test and reference formulations for plasma levels of ursodiol in AUC_{0-24}, AUC_{0-48} and AUC_{0-72} and a 3.5% difference in C_{max}. The 90% shortest confidence intervals for ursodiol, using least squares means, are presented below:

		90% CI [log-transformed]
Unconjugated ursodiol	AUC_{0-24} (n=24)	[92.0; 113.8]
	AUC_{0-48} (n=24)	[82.9; 114.5]
	AUC_{0-72} (n=23)	[84.8; 113.0]
	C_{max} (n=24)	[93.3; 122.0]
Total ursodiol	AUC_{0-24} (n=24)	[96.8; 119.3]
	AUC_{0-48} (n=24)	[91.6; 119.1]
	AUC_{0-72} (n=24)	[91.0; 118.5]
	C_{max} (n=24)	[91.4; 116.8]

In-vitro Dissolution:

The sponsor has conducted dissolution testing with test/reference bio-lots used in this study, using the current USP dissolution method. The resultant summaries are attached.

Potency:

The assay for potency of the Amide product was 103.3% of label claim [C.U. was 103.8% of LC; ave. of 10, CV=0.6%. No potency or content uniformity data could be found for Actigall.

Batch Size:

The batch size for the bio-batch of Amide's 300 mg ursodiol capsule was 125,000 dosage units.

Comment:

1. The complete analytical method was not submitted. The sponsor should submit the standard and QC sample preparation procedure as well as sample, standard, and QC processing procedures for both unconjugated ursodiol [SOP No. GC-M-5841-00] and total ursodiol [SOP No. GC-M-5862-01].

2. In the analysis of **total ursodiol**, the sponsor should explain why two sets of QC samples were prepared and run as noted on page 1435 of vol. 1.4 (covering curve code HUD 13-53) and on page 1437 of vol. 1.4 (covering curve code HUD 56-74). It was noted that there was only one set of corresponding calibration curve standards (pp 1438-40, vol. 1.4).

3. The sponsor should explain why ursodiol-glycine was used in the spiking of QC samples in the analysis of total ursodiol.

4. Samples were analyzed for **unconjugated ursodiol** between Jan 5, 1998 and Oct 26, 1998; yet long term stability data was provided for a period of only 21 days. The sponsor needs to provide long term stability data to cover the length of the entire study.

5. Long term stability data was not submitted for **total ursodiol**. The sponsor should submit such data that covers the duration of the study.

6. The sponsor did not provide the raw data for 'C_{max}' samples to document lack of interference at the retention time of the internal standard. The sponsor should provide such documentation for both the unconjugated and total ursodiol analyses.

7. Potency/content uniformity data was not provided for the reference product used in this study. The sponsor should submit such data.

8. The sponsor is requested to submit on diskette all baseline uncorrected subject data for unconjugated and total ursodiol [including period, sequence, treatment for the PK parameters and the individual sample concentration values for each subject arranged sequentially in a flat ascii text format]; baseline values as well as the zero hour value (before baseline correction) for each subject should also be included in the dataset.

Recommendation:

1. The bioequivalence study conducted by Phoenix International Life Sciences for Amide Pharmaceuticals Inc. on their ursodiol 300 mg capsule is incomplete per comments #1-8.

Comments #1-8 should be forwarded to the sponsor.

R. Lee 3/1/99

J. Lee
Division of Bioequivalence
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

/S/ 3/4/1999

Concur: /S/ Date: 3/9/99

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

JLee/jl/03-01-99

USP XXIII Apparatus II Basket _____ Paddle x rpm 75

Medium: pH 8.4 phosphate buffer Volume: 1000 ml

Number of Tabs/Caps Tested: 12

Reference Drug: Actigall, 300 mg capsule [Novartis]

Assay Methodology: LC

Results

Time (min)	Test Product Lot # 6123A Mean % Dissolved	Range	(CV)	Reference Product Lot # 1432 Mean % Dissolved	Range	(CV)
15	72.0		(3.6)	71.9		(3.0)
20	84.7		(1.6)	81.4		(1.6)
30	97.6		(1.5)	90.5		(1.4)
			( )			( )
			( )			( )
			( )			( )
	Lot #			Lot #		
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )
			( )			( )

Mean Unconjugated Ursodiol Levels (Baseline adj.)
(ng/ml)

Amide

Time (hr)	N	Mean	Std Dev	CV
0	24	0	0	.
0.5	24	643.03	615.65	95.7
1	24	1386.13	1261.19	91.0
1.5	24	1734.14	1125.21	64.9
2	24	1795.76	970.62	54.1
2.5	24	1583.74	833.87	52.7
3	24	1440.75	689.89	47.9
3.5	24	1220.28	630.11	51.6
4	24	966.55	469.82	48.6
5	24	680.02	694.03	102.1
6	24	365.86	446.19	122.0
7	24	210.02	250.14	119.1
8	24	121.59	159.09	130.8
9	24	72.77	120.33	165.4
10	24	97.085	113.82	117.2
12	24	92.88	220.12	237.0
14	24	248.53	292.86	117.8
16	24	345.88	340.79	98.5
24	24	41.36	170.03	411.1
36	24	341.71	518.35	151.7
48	24	49.48	48.46	97.9
72	24	137.21	181.69	132.4

Actigall

Time (hr)	N	Mean	Std Dev	CV
0	24	0	0	.
0.5	24	447.27	485.78	108.6
1	24	814.42	724.66	89.0
1.5	24	1296.32	1331.66	102.7
2	24	1395.28	973.06	69.7
2.5	24	1496.71	888.90	59.4
3	24	1397.87	797.45	57.0
3.5	24	1308.44	721.79	55.2
4	24	1097.49	643.56	58.6
5	24	780.75	644.86	82.6
6	24	413.35	417.17	100.9
7	24	232.39	289.22	124.5
8	24	169.09	187.24	110.7
9	24	124.37	213.65	171.8
10	24	109.32	151.68	138.8
12	24	163.62	220.29	134.6
14	24	421.17	519.01	123.2
16	24	402.63	472.43	117.3
24	24	92.24	103.72	112.4
36	24	445.11	536.30	120.5
48	24	53.94	43.79	81.2
72	24	79.41	300.51	378.4

Mean Total Ursodiol Levels (Baseline adj.)
(ng/ml)

Amide

Time (hr)	N	Mean	Std Dev	CV
0	24	0	0	.
0.5	24	620.86	569.98	91.8
1	24	1371.99	1281.52	93.4
1.5	24	1741.65	1211.63	69.6
2	24	1844.08	1021.14	55.4
2.5	24	1651.81	899.44	54.5
3	23	1657.42	870.93	52.5
3.5	24	1484.85	782.87	52.7
4	24	1220.61	689.365	56.5
5	24	1539.56	1010.12	65.6
6	24	1064.5	607.72	57.1
7	24	955.70	525.43	55.0
8	24	701.41	425.05	60.6
9	24	625.52	424.10	67.8
10	24	1080.09	914.45	84.7
12	24	778.54	553.99	71.2
14	24	1044.35	721.24	69.1
16	24	778.13	524.40	67.4
24	24	279.78	401.06	143.3
36	24	984.96	796.10	80.8
48	24	291.95	365.72	125.3
72	24	318.74	293.09	92.0

Actigall

Time (hr)	N	Mean	Std Dev	CV
0	24	0	0	.
0.5	24	401.35	501.79	125.0
1	24	819.84	828.75	101.1
1.5	24	1349.16	1497.89	111.0
2	24	1425.88	1134.61	79.6
2.5	24	1673.35	1238.23	74.0
3	24	1600.99	994.86	62.1
3.5	24	1451.07	802.26	55.3
4	24	1235.43	704.91	57.1
5	24	1475.81	878.06	59.5
6	24	976.27	455.27	46.6
7	24	836.09	418.85	50.1
8	24	724.58	394.87	54.5
9	24	595.98	350.62	58.8
10	24	806.56	480.41	59.6
12	23	693.92	420.95	60.7
14	24	990.57	582.45	58.8
16	24	804.41	547.18	68.0
24	24	269.46	327.13	121.4
36	23	1026.04	679.93	66.3
48	24	169.30	240.48	142.0
72	24	265.67	428.86	161.4

Table 1
Project No: 971230
Summary of Results - Unconjugated Ursodiol in Plasma
Pharmacokinetic Parameters
(N = 24)

	ln AUC 0-24* (ng·h/mL)	ln AUC 0-48* (ng·h/mL)	ln AUC 0-72* (ng·h/mL)	ln Cmax* (ng/mL)	tmax (h)
Amide (A)					
Mean	9902.98	14092.32	15991.88	2176.2913	3.917
CV	37.1	44.2	47.3	61.9	176.7
n	23	23	23	24	24
Ciba Geneva (B)					
Mean	9399.85	14245.97	16380.40	2039.7409	4.104
CV	46.8	59.4	59.9	48.5	167.5
n	24	24	23	24	24
Least-Squares Means					
Amide (A)	9615.35	13881.37	15936.00	2176.2913	
Ciba Geneva (B)	9399.85	14245.97	16275.30	2039.7410	
Ratio of Least-Squares Means (A/B)%	102.3	97.4	97.9	106.7	
90% Confidence Intervals (A/B)%					
lower limit:	92.0%	82.9%	84.8%	93.3%	
upper limit:	113.8%	114.5%	113.0%	122.0%	
p-Value (ANOVA)					
A vs B	0.7170	0.7847	0.8033	0.4149	
Period	0.6639	0.5023	0.4277	0.8276	
Sequence	0.0382	0.1061	0.2462	0.0761	

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
See Section 3 of Report for details on calculation of parameters.
PhAST STAB 2.3-000

Table 1
Project No: 971230
Summary of Results - Unconjugated Ursodiol in Plasma
Pharmacokinetic Parameters
(N = 24)

	ln AUC 0-24* (ng·h/mL)	ln AUC 0-48* (ng·h/mL)	ln AUC 0-72* (ng·h/mL)	ln Cmax* (ng/mL)	tmax (h)
Power					
A vs B (REF=B)	93.0%	61.7%	72.0%	78.0%	
Intrasubject CV%	21.1	32.6	28.9	27.5	

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
See Section 3 of Report for details on calculation of parameters.
PhAST STAB 2.3-000

Table 2
Project No: 971230
Summary of Results - Total Ursodiol in Plasma
Pharmacokinetic Parameters
(N = 24)

	ln AUC 0-24* (ng·h/mL)	ln AUC 0-48* (ng·h/mL)	ln AUC 0-72* (ng·h/mL)	ln Cmax* (ng/mL)	tmax (h)
Amide (A)					
Mean	20182.42	33495.58	34749.96	2422.7868	4.229
CV	50.1	55.3	101.0	63.6	163.1
n	23	23	24	24	24
Ciba Geneva (B)					
Mean	17638.92	30977.94	33460.50	2341.4884	7.021
CV	53.2	47.0	77.3	46.6	160.1
n	24	24	24	24	24
Least-Squares Means					
Amide (A)	18952.28	32362.19	34749.96	2422.7868	
Ciba Geneva (B)	17638.92	30977.94	33460.50	2341.4884	
Ratio of Least-Squares Means (A/B)%	107.4	104.5	103.9	103.5	
90% Confidence Intervals (A/B)%					
lower limit:	96.8%	91.6%	91.0%	91.6%	
upper limit:	119.3%	119.1%	118.5%	116.8%	
p-Value (ANOVA)					
A vs B	0.2510	0.5731	0.6283	0.6343	
Period	0.6843	0.6824	0.9998	0.5157	
Sequence	0.1617	0.4343	0.3571	0.1899	

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
See Section 3 of Report for details on calculation of parameters.
PhAST STAB 2.3-000

Table 2
Project No: 971230
Summary of Results - Total Ursodiol in Plasma
Pharmacokinetic Parameters
(N = 24)

	ln AUC 0-24* (ng·h/mL)	ln AUC 0-48* (ng·h/mL)	ln AUC 0-72* (ng·h/mL)	ln Cmax* (ng/mL)	tmax (h)
Power					
A vs B (REF=B)	93.6%	79.5%	79.0%	85.4%	
Intrasubject CV%	20.8	26.3	27.2	24.9	

* For ln-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported.
See Section 3 of Report for details on calculation of parameters.
PhAST STAB 2.3-000

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:75-517 APPLICANT: Amide Pharmaceuticals

DRUG PRODUCT: Ursodiol 300 mg capsule

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. The complete analytical method was not submitted. Please submit the standard and QC sample preparation procedure as well as sample, standard, and QC processing procedures for both unconjugated ursodiol [SOP No. GC-M-5841-00] and total ursodiol [SOP No. GC-M-5862-01].

2. In the analysis of **total ursodiol**, explain why two sets of QC samples were prepared and run as noted on page 1435 of vol. 1.4 (covering curve code HUD 13-53) and on page 1437 of vol. 1.4 (covering curve code HUD 56-74). It was noted that there was only one set of corresponding calibration curve standards (pp 1438-40, vol. 1.4).

3. Please explain why ursodiol-glycine was used in the spiking of QC samples in the analysis of total ursodiol.

4. Samples were analyzed for **unconjugated ursodiol** between Jan 5, 1998 and Oct 26, 1998; yet long term stability data was provided for a period of only 21 days. You need to provide long term stability data to cover the length of the entire study.

5. Long term stability data was not submitted for **total ursodiol**. Please submit such data that covers the duration of the study.

6. You did not provide the raw data for 'C_{max}' samples to document lack of interference at the retention time of the internal standard. Please provide such documentation for both the unconjugated and total ursodiol analyses.

7. Potency/content uniformity data was not provided for the reference product used in this study. Please submit such data.

8. Please submit on diskette all baseline uncorrected subject data for unconjugated and total ursodiol [including period, sequence, treatment for the PK parameters and the individual sample concentration values for each subject arranged sequentially in a flat ascii text format]; **baseline values** as well as the zero hour value (before baseline correction) for each subject should also be included in the dataset.

Sincerely yours,

/S/

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

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:75-517 APPLICANT: Amide Pharmaceuticals

DRUG PRODUCT: Ursodiol 300 mg capsule

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. The complete analytical method was not submitted. Please submit the standard and QC sample preparation procedure as well as sample, standard, and QC processing procedures for both unconjugated ursodiol [SOP No. GC-M-5841-00] and total ursodiol [SOP No. GC-M-5862-01].

2. In the analysis of **total ursodiol**, explain why two sets of QC samples were prepared and run as noted on page 1435 of vol. 1.4 (covering curve code HUD 13-53) and on page 1437 of vol. 1.4 (covering curve code HUD 56-74). It was noted that there was only one set of corresponding calibration curve standards (pp 1438-40, vol. 1.4).

3. Please explain why ursodiol-glycine was used in the spiking of QC samples in the analysis of total ursodiol when ursodiol was used in spiking the QC samples in the analysis of unconjugated ursodiol.

4. Samples were analyzed for **unconjugated ursodiol** between Jan 5, 1998 and Oct 26, 1998; yet long term stability data was provided for a period of only 21 days. You need to provide long term stability data to cover the length of the entire study.

5. Long term stability data was not submitted for **total ursodiol**. Please submit such data that covers the duration of the study.

6. You did not provide the raw data for 'C_{max}' samples to document lack of interference at the retention time of the internal standard. Please provide such documentation for both the unconjugated and total ursodiol analyses.

7. Potency/content uniformity data was not provided for the reference product used in this study. Please submit such data.

8. Please submit on diskette all baseline uncorrected subject data for unconjugated and total ursodiol [including period, sequence. treatment for the PK parameters and the individual sample concentration values for each subject arranged sequentially in a flat ascii text format]; **baseline values** as well as the zero hour value (before baseline correction) for each subject should also be included in the dataset.

Sincerely yours,

/S/

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

Page(s) 1

Contain Trade Secret,

Commercial/Confidential

Information and are not

releasable.

Composition,

see labeling for

releasable information

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA:75-517 APPLICANT: Amide Pharmaceuticals 24

DRUG PRODUCT: Ursodiol 300 mg capsule

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. The complete analytical method was not submitted. Please submit the standard and QC sample preparation procedure as well as sample, standard, and QC processing procedures for both unconjugated ursodiol [SOP No. GC-M-5841-00] and total ursodiol [SOP No. GC-M-5862-01].

2. In the analysis of **total ursodiol**, explain why two sets of QC samples were prepared and run as noted on page 1435 of vol. 1.4 (covering curve code HUD 13-53) and on page 1437 of vol. 1.4 (covering curve code HUD 56-74). It was noted that there was only one set of corresponding calibration curve standards (pp 1438-40, vol. 1.4).

3. Please explain why ursodiol-glycine was used in the spiking of QC samples in the analysis of total ursodiol.

4. Samples were analyzed for **unconjugated ursodiol** between Jan 5, 1998 and Oct 26, 1998; yet long term stability data was provided for a period of only 21 days. You need to provide long term stability data to cover the length of the entire study.

5. Long term stability data was not submitted for **total ursodiol**. Please submit such data that covers the duration of the study.

6. You did not provide the raw data for 'C_{max}' samples to document lack of interference at the retention time of the internal standard. Please provide such documentation for both the unconjugated and total ursodiol analyses.

7. Potency/content uniformity data was not provided for the reference product used in this study. Please submit such data.

8. Please submit on diskette all <u>baseline uncorrected</u> subject data for unconjugated and total ursodiol [including period, sequence, treatment for the PK parameters and the individual sample concentration values for each subject arranged sequentially in a flat ascii text format]; **baseline values** as well as the zero hour value (before baseline correction) for each subject should also be included in the dataset.

Sincerely yours,

/S/

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

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 75-517

CORRESPONDENCE

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

November 30, 1999

NC

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Control Room 150, HFD-630
Metropark North II
7500 Standish Place
Rockville, MD 20855

AMENDMENT

RE: ANDA - 75-517
Ursodiol Capsules USP

Dear Mr. Sporn:

In reference to my telephone conversation with Mr. Reed Brown, enclosed is a revised copy of the September 30, 1999 cover letter for ANDA 75-517. Ursodiol Capsules, USP.

The correct change in specifications for [redacted] %.

Please forward any communication regarding this ANDA to me at the above address. If you need to call or fax me, my telephone number is (973) 890-1440 and Fax number is (973) 890-7980.

Sincerely
Amide Pharmaceutical, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs.

Enc.

CENTER FOR DRUG EVALUATION AND RESEARCH
DEC 01 1999
CDD

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424
Telephone (973) 890-1440
Fax (973) 890-7980

September 30, 1999

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Document Control Room 150, HFD-630
Metropark North II
7500 Standish Place
Rockville, MD 20855

AMENDMENT

RE: ANDA – 75-517
Ursodiol Capsules USP

Dear Mr. Sporn:

In reference to the changes in the manufacturers specification for the drug substance, for our pending ANDA 75-517, Ursodiol Capsules, USP Amide is submitting this amendment.

Following changes are made for the test and specification of the active Ursodiol, USP:

1. widened the ; to match the limit as per USP
2. removed the TLC method for identification test, as Identification test will be performed via IR testing.

Enclosed is a copy of Amide test specification for Ursodiol and the manufacturers certificate of analysis.

Please forward any communication regarding this ANDA to me at the above address. If you need to call or fax me, my telephone number is (973) 890-1440 and Fax number is (973) 890-7980.

Sincerely
Amide Pharmaceutical, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs.

Enc.

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

January 19, 1999

NDA ORIG AMENDMENT
NEW CORRESP
W/AB
NC

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

PAPER AND ELECTRONIC

RE: ANDA - 75-~~513~~ 517 ORIGINAL APPLICATION
Ursodiol Capsules USP

Dear Mr. Sporn:

Amide Pharmaceutical, Inc. ("AMIDE") submits today an electronic application ("ANDA") seeking approval to market Ursodiol Capsules.

The Original application for this product was submitted to FDA on December 5, 1998. Enclosed is electronic version of the application.

Included in the file are:

1. Signed Form 356h
2. Signed certificate stating the data in the electronic portion of the application is same as the paper copy to the best of our knowledge.
3. Following Compact disks:
   a. 2 CD's both CD's consist of all information required by EVA, Companion document for CMC and BA/BE. The contents and file names are attached on page 2.
4. Also, enclosed is the bioequivalency companion document, submission information and Certification from (2 copies)

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

RECEIVED
JAN 19 1999
GENERIC DRUGS

Enc.

AMIDE PHARMACEUTICAL, INC.

Ursodiol Capsules

CERTIFICATION LETTER

We hereby certify that, to the best of our knowledge, data contained in the electronic submission are identical to or derived from the information in the hard copy submission, as indicated in the Companion Document for our ANDA 75-513 Ursodiol Capsules.

Jasmine Shah, M.S., R.Ph.
Director-Regulatory Affairs

Date 1/19/99

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 074
Telephone (973) 890-1440
Fax (973) 890-7980

December 17, 1998

NEW CORRESP
NC

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

PAPER AND ELECTRONIC

RE: ANDA 75-517
Ursodiol Capsules USP

Dear Mr. Sporn:

In reference to my telephone conversation with Ms. Carol Holquist, enclosed find the following in reference to our ANDA Application for Ursodiol Capsules:

1. DMF Authorization letter from the manufacturer of the active ingredient (Erregierre), authorizing the supplier (SST Corporation) to issue the DMF Referral letter.
2. Revised Sample Statement.

Please direct any written communications regarding this ANDA to me at the above address. If you need to call or fax me, my phone numbers are 973-890-1440 and 973-890-7980 (fax).

Sincerely,
Amide Pharmaceutcial, Inc.

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs

RECEIVED
JAN 0 6 1999
GENERIC DRUGS

Enc.

1-13-99

ANDA 75-517

Amide Pharmaceutical, Inc.
Attention: Jasmine Shah
101 East Main Street
Little Falls, NJ 07424

DEC 29 1998

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 the telephone conversation dated December 5, 1998 and your correspondence dated December 17, 1998.

NAME OF DRUG: Ursodiol Capsules USP, 300 mg

DATE OF APPLICATION: December 7, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 7, 1998

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

/S/

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

T551

Amide
PHARMACEUTICAL, INC.

101 East Main Street
Little Falls, New Jersey 07424

Telephone (973) 890-1440
Fax (973) 890-7980

December 7, 1998

Douglas Sporn
Director
Office of Generic Drugs
CDER, FDA
Metropark North II
7500 Standish Place, Room 150
Rockville, MD 20855

PAPER AND ELECTRONIC

RE: ANDA - ORIGINAL APPLICATION
Ursodiol Capsules

Dear Mr. Sporn:

Enclosed please find Amide Pharmaceutical's original Drug Application for Ursodiol Capsules and a transmittal letter (and one copy) describing same.

Kindly, have the copy of the transmittal letter stamped "filed" and return it to our courier who has been instructed to wait.

Thank you for your attention to this matter.

Very truly yours,

Jasmine Shah, MS, R.Ph.
Director Regulatory Affairs