LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

1600 STEWART AVENUE, WESTBURY, NY 11590
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March 3, 2003

0933 '03 MAR -4 A9:24

(OVERNIGHT COURIER 3/3/03)

Dockets Management Branch, HFA-305
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

The undersigned submits this petition in quadruplicate pursuant to 505 (j) (2) (C) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 10.20 and 10.30 to request the Commissioner of the Food and Drug Administration to make a determination that an Abbreviated New Drug Application (ANDA) may be submitted for Ursodiol Oral Suspension, 20 mg/mL in a ready-to-use form for oral administration.

A. Action Requested

The petitioner requests that the Commissioner of the Food and Drug Administration make a determination that the drug product, Ursodiol Oral Suspension, 20 mg/mL, is suitable for evaluation under an ANDA. The referenced product is Actigall® Ursodiol Oral Capsule, 300 mg (NDA 19-594). This Petition requests a change in dosage form from that of the approved capsule to a liquid form.

B. Statement of Grounds

The Federal Food, Drug and Cosmetic Act provides for the submission of an ANDA for a drug that differs in dosage form from a listed drug, provided the FDA has approved a petition that proposed filing of such an application. This petition involves a change in dosage form from that of the listed drug. The proposed drug product is equivalent in use, dosage and route of administration to the listed drug, Actigall® (Ursodiol Oral Capsule, 300 mg). This petition proposes to market an oral suspension as an alternative dosage form providing for greater compliance for patients who have difficulty swallowing, or cannot swallow capsules, and for ease of titration while seeking the effective dose level. Dosing of Ursodiol in treatment of radiolucent gallbladder stones is 8-10 mg/kg/day given in two or three divided doses. A suspension dosage form will allow for optimal dosage titration for each patient for dissolution of gallstones. A suspension dosage will also allow practitioners to titrate to the lowest effective dose, which may decrease adverse reactions commonly experienced with the capsule dosage form.

Finally, the labeling for the proposed product is the same as the reference-listed drug, except for the change in strength and dosage form reflected in this petition. The draft labeling and approved labeling for the reference-listed drug are attached.

03P.0082

QP1

C. Environmental Impact

An environmental assessment on the action requested in this petition qualifies for a categorical exclusion from the requirements of an environmental assessment or impact statement under 21 CFR 25.31(a).

D. Economic Impact

Pursuant to 21 CFR 10.30(b), economic impact information is to be submitted when requested by the Commissioner. Information will be promptly submitted, if requested.

E. Certification

Lachman Consultant Services, Inc. certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

Gordon Johnston (BH)

Gordon R. Johnston
Associate

GJ/bh

Attachments: *1) Draft Labeling*
2) Actigall Package Insert Labeling

cc: M. Shimer
G. Davis, OGD
L. Lachman
R. Pollock

P01k3062

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 1

9. Keep the patch dry, if possible, to prevent if from falling off. Limited contact with water, however, as in bathing or swimming, will not affect the system. In the unlikely event that the patch falls off, throw it away and put a new one behind the other ear.

This leaflet presents a summary of information about Transderm Scōp. If you would like more information or if you have any questions, ask your doctor or pharmacist. A more technical leaflet is available, written for your doctor. If you would like to read the leaflet, ask your pharmacist to show you a copy. You may need the help of your doctor or pharmacist to understand some of the information.

Distributed by:
Novartis Consumer Health, Inc.
Summit, N.J. 07901-1312

Shown in Product Identification Guide, page 324

Novartis Pharmaceuticals Corporation

NOVARTIS PHARMACEUTICALS CORPORATION
59 Route 10
East Hanover, NJ 07936
(for branded products)

GENEVA PHARMACEUTICALS, INC.
A NOVARTIS COMPANY
2655 West Midway Boulevard
PO Box 446
Broomfield, CO 80038-0446
(for branded generic product listing refer to Geneva Pharmaceuticals, Inc.)

For Information Contact (*branded products*):
Customer Response Department
(888) NOW-NOVARTIS (888-669-6682)
Global Internet Address:
http://www.novartis.com

For Information Contact (*branded generic products*):
Customer Support Department
(800) 525-8747
(303) 466-2400
FAX: (303) 469-6467

~~ACTIGALL®~~ ℞
~~(act-i-gall)~~
ursodiol USP
~~Capsules~~ oral suspension
~~Caution: Federal law prohibits dispensing without prescription.~~ Rx only
~~The following prescribing information is based on official labeling in effect on August 1, 1998.~~

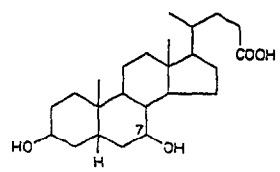
SPECIAL NOTE

Gallbladder stone dissolution with ~~Actigall~~ 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

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

~~Actigall~~ 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, methanol, and glacial acetic acid; sparingly soluble in chloroform; slightly soluble in ether; and 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 structure is shown below:



Inactive Ingredients. Colloidal silicon dioxide, ferric oxide, gelatin, magnesium stearate, starch (corn), and titanium dioxide.

CLINICAL PHARMACOLOGY

About 90% of a therapeutic dose of ~~Actigall~~ 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., 15-18 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%-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 6-78 months with ~~Actigall~~ doses ranging from about 5 to 20 mg/kg/day, an ~~Actigall~~ dose of about 8-10 mg/kg/day appeared to be the best dose. With an Actigall 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 8 of patients with stones up to 5 mm in diameter. Age, weight, degree of obesity, and serum cholesterol level not related to the chance of stone dissolution with Actig A nonvisualizing gallbladder by oral cholecystogram pre the initiation of therapy is not a contraindication to Acti therapy (the group of patients with nonvisualizing gallb ders in the ~~Actigall~~ studies had complete stone dissolu rates similar to the group of patients with visualizing g bladders). However, gallbladder nonvisualization devel ing during ursodiol treatment predicts failure of compl stone dissolution and in such cases therapy should discontinued.

Partial stone dissolution occurring within 6 months beginning therapy with ~~Actigall~~ appears to be associat with a >70% chance of eventual complete stone dissolut with further treatment; partial dissolution observ within 1 year of starting therapy indicates a 40% prob bility of complete dissolution.

Stone recurrence after dissolution with ~~Actigall~~ therapy w seen within 2 years in 8/27 (30%) of patients in the U studies. Of 16 patients in the U.K. study whose stones h previously dissolved on chenodiol but later recurred, 11 h complete dissolution on Actigall. Stone recurrence has be observed in up to 50% of patients within 5 years of comple stone dissolution on ursodiol therapy. Serial ultrason graphic examinations should be obtained to monitor f recurrence of stones, bearing in mind that radiolucency the stones should be established before another course Actigall is instituted. A prophylactic dose of Actigall has n been established.

Gallstone Prevention

Two placebo-controlled, multicenter, double-blind, randon ized, parallel group trials in a total of 1316 obese patien were undertaken to evaluate ~~Actigall~~ in the prevention gallstone formation in obese patients undergoing rap weight loss. The first trial consisted of 1004 obese patien with a body mass index (BMI) ≥38 who underwent weigl loss induced by means of a very low calorie diet for a perio of 16 weeks. An intent-to-treat analysis of this trial showe that gallstone formation occurred in 23% of the placeb group, while those patients on 300, 600, or 1200 mg/day Actigall experienced a 6%, 3%, and 2% incidence of gal stone formation, respectively. The mean weight loss for th 16-week trial was 47 lb for the placebo group, and 47, 4 and 50 lb for the 300, 600, and 1200 mg/day Actigall group respectively.

The second trial consisted of 312 obese patients (BMI ≥40 who underwent rapid weight loss through gastric bypas surgery. The trial drug treatment period was for 6 month following this surgery. Results of this trial showed that gall stone formation occurred in 23% of the placebo group, whil those patients on 300, 600, or 1200 mg/day of Actigall expe rienced a 9%, 1%, and 5% incidence of gallstone formation respectively. The mean weight loss for this 6-month tria was 64 lb for the placebo group, and 67, 74, and 72 lb for the 300, 600, and 1200 mg/day Actigall 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	17.34	58.82

Continued on next page

Actigall—Cont.

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. Actigall 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 Actigall beyond 24 months is not established.
2. Actigall is indicated for the prevention of gallstone formation in obese patients experiencing rapid weight loss.

CONTRAINDICATIONS

1. Actigall will not dissolve calcified cholesterol stones, radiopaque stones, or radiolucent bile pigment stones. Hence, patients with such stones are not candidates for Actigall 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 Actigall 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 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 Actigall therapy and, in fact, Actigall has been shown to decrease liver enzyme levels in liver disease. However, patients given Actigall 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 Actigall by reducing its absorption. Aluminum-based antacids have been shown to adsorb bile acids in vitro and may be expected to interfere with Actigall 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 Actigall.

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 Actigall 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 Actigall is administered to a nursing mother.

Pediatric Use

The safety and effectiveness of Actigall 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 8-10 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

	Actigall 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 Actigall has been reported. Doses of Actigall in the range 16-20 mg/kg/day have been tolerated for 6-37 months without symptoms by 7 patients. The LD_{50} for ursodiol in rats over 5000 mg/kg given over 7-10 days and over 7500 mg for mice. The most likely manifestation of severe overdose with Actigall would probably be diarrhea, which should be treated symptomatically.

DOSAGE AND ADMINISTRATION

Gallstone Dissolution

The recommended dose for Actigall treatment of radiolucent gallbladder stones is 8-10 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 Actigall therapy to monitor gallstone response. If gallstones appear to have dissolved, Actigall 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 Actigall therapy, the likelihood of success is greatly reduced.

Gallstone Prevention

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

HOW SUPPLIED

~~Capsules 300 mg — opaque, white, pink (imprinted Actigall 300 mg)~~
~~Bottles of 100 ..... NDC 0078-0319-01~~
~~Do not store above 86°F (30°C).~~
~~Dispense in tight container (USP).~~

~~C97-12 (Rev. 12/97)~~

~~Distributed by~~
~~Novartis Pharmaceuticals Corporation~~
~~East Hanover, New Jersey 07936~~
~~Shown in Product Identification Guide, page 324~~

ANAFRANIL®

[ana fränill]
clomipramine hydrochloride
Capsules

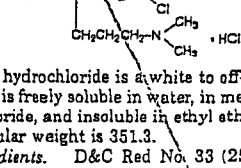
Caution: Federal law prohibits dispensing without prescription.

The following prescribing information is based on official labeling in effect on August 1, 1998.

DESCRIPTION

Anafranil, clomipramine hydrochloride, is an antiobsessional drug that belongs to the class (dibenzazepine) of pharmacologic agents known as tricyclic antidepressants. Anafranil is available as capsules of 25, 50, and 75 mg for oral administration.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethylamino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine monohydrochloride and its structural formula is



Clomipramine hydrochloride is a white to off-white crystalline powder. It is freely soluble in water, in methanol, and in methylene chloride, and insoluble in ethyl ether and in hexane. Its molecular weight is 351.3.

Inactive Ingredients. D&C Red No. 33 (25-mg capsules only), D&C Yellow No. 10, FD&C Blue No. 1 (50-mg capsules only), FD&C Yellow No. 6, gelatin, magnesium stearate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clomipramine (CMI) is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but CMI's capacity to inhibit the reuptake of serotonin (5-HT) is thought to be important.

Citizen Petition
Ursodiol for Oral Administration

Labeling for petitioner's product:
Ursodiol Oral Suspension, 20 mg/mL

[1] Reference Drug: states drug tradename, "Actigall"
Petitioner: will use generic drug name "ursodiol" in place of tradename

[2] Reference Drug: states outdated federal caution statement
Petitioner: will replace federal caution statement with "Rx only"

[3] Reference Drug: dosage form stated as "capsules"
Petitioner: will change dosage form to "oral suspension"

[4] Reference Drug: How Supplied section states information on capsule product
Petitioner: How Supplied section states information on suspension product (storage conditions will be revised accordingly but have not yet been determined for the proposed suspension)

[5] Reference Drug: states information about distributor Novartis
Petitioner: will state information about manufacturer of the suspension

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 2

Citizen Petition
Ursodiol for Oral Administration

Labeling for reference product:

Actigall® Ursodiol Oral Capsule, 300 mg (NDA 19-594)

9. Keep the patch dry, if possible, to prevent if from falling off. Limited contact with water, however, as in bathing or swimming, will not affect the system. In the unlikely event that the patch falls off, throw it away and put a new one behind the other ear.

This leaflet presents a summary of information about Transderm Scop. If you would like more information or if you have any questions, ask your doctor or pharmacist. A more technical leaflet is available, written for your doctor. If you would like to read the leaflet, ask your pharmacist to show you a copy. You may need the help of your doctor or pharmacist to understand some of the information.

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Shown in Product Identification Guide, page 324

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http: //www.novartis.com

For Information Contact (*branded generic products*):

Customer Support Department
(800) 525-8747
(303) 466-2400
FAX: (303) 469-6467

ACTIGALL®

℞

[ăct-ĭ-găll]
ursodiol USP
Capsules

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The following prescribing information is based on official labeling in effect on August 1, 1998.

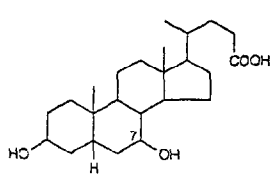
SPECIAL NOTE

Gallbladder stone dissolution with Actigall 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

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

Actigall 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, methanol, and glacial acetic acid; sparingly soluble in chloroform; slightly soluble in ether; and 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 structure is shown below:



Inactive Ingredients. Colloidal silicon dioxide, ferric oxide, gelatin, magnesium stearate, starch (corn), and titanium dioxide.

CLINICAL PHARMACOLOGY

About 90% of a therapeutic dose of Actigall 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., 15-18 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%-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 6-78 months with Actigall doses ranging from about 5 to 20 mg/kg/day, an Actigall dose of about 8-10 mg/kg/day appeared to be the best dose. With an Actigall 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 31% 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 Actigall.

A nonvisualizing gallbladder by oral cholecystogram prior to the initiation of therapy is not a contraindication to Actigall therapy (the group of patients with nonvisualizing gallbladders in the Actigall 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 Actigall 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 Actigall 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 Actigall. 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 Actigall is instituted. A prophylactic dose of Actigall 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 Actigall 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 Actigall 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 Actigall 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 Actigall 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 Actigall 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

Continued on next page

Actigall—Cont.

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. Actigall 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 Actigall beyond 24 months is not established.
2. Actigall is indicated for the prevention of gallstone formation in obese patients experiencing rapid weight loss.

CONTRAINDICATIONS

1. Actigall will not dissolve calcified cholesterol stones, radiopaque stones, or radiolucent bile pigment stones. Hence, patients with such stones are not candidates for Actigall 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 Actigall 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 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 Actigall therapy and, in fact, Actigall has been shown to decrease liver enzyme levels in liver disease. However, patients given Actigall 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 Actigall by reducing its absorption. Aluminum-based antacids have been shown to adsorb bile acids in vitro and may be expected to interfere with Actigall 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 Actigall.

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 Actigall 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 Actigall is administered to a nursing mother.

Pediatric Use

The safety and effectiveness of Actigall 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 8-10 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

	Actigall 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 Actiga has been reported. Doses of Actigall in the range o 16-20 mg/kg/day have been tolerated for 6-37 months with out symptoms by 7 patients. The LD_{50} for ursodiol in rats over 5000 mg/kg given over 7-10 days and over 7500 mg/k for mice. The most likely manifestation of severe overdos with Actigall would probably be diarrhea, which should b treated symptomatically.

DOSAGE AND ADMINISTRATION

Gallstone Dissolution

The recommended dose for Actigall treatment of radiolucen gallbladder stones is 8-10 mg/kg/day given in 2 or 3 divide doses.

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

Gallstone Prevention

The recommended dosage of Actigall for gallstone prevei tion in patients undergoing rapid weight loss is 600 mg/da (300 mg b.i.d.).

HOW SUPPLIED

Capsules 300 mg — opaque, white, pink (imprinted Actiga 300 mg)

Bottles of 100 ..... NDC 0078-0319-0

Do not store above 86°F (30°C).

Dispense in tight container (USP).

C97-12 (Rev. 12/97

Distributed by
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

Shown in Product Identification Guide, page 324

ANAFRANIL®

[ana frănill]

clomipramine hydrochloride

Capsules

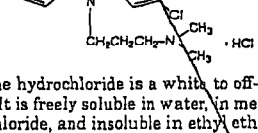
Caution: Federal law prohibits dispensing without prescription.

The following prescribing information is based on officia labeling in effect on August 1, 1998.

DESCRIPTION

Anafranil, clomipramine hydrochloride, is an antiobses sional drug that belongs to the class (dibenzazepine) o pharmacologic agents known as tricyclic antidepressants Anafranil is available as capsules of 25, 50, and 75 mg fo oral administration.

Clomipramine hydrochloride is 3-chloro-5-[3-(dimethyl amino)propyl]-10,11-dihydro-5H-dibenz[b,f]azepine mono hydrochloride and its structural formula is



Clomipramine hydrochloride is a white to off-white crystal line powder. It is freely soluble in water, in methanol, and i methylene chloride, and insoluble in ethyl ether and in hex ane. Its molecular weight is 351.3.

Inactive Ingredients. D&C Red No. 33 (25-mg capsule only), D&C Yellow No. 10, FD&C Blue No. 1 (50-mg cap sules only), FD&C Yellow No. 6, gelatin, magnesium stea rate, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, starch, and titanium dioxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Clomipramine (CMI) is presumed to influence obsessive and compulsive behaviors through its effects on serotonergic neuronal transmission. The actual neurochemical mechanism is unknown, but CMI's capacity to inhibit the reuptake of serotonin (5-HT) is thought to be important.